Pharmaceutical Treatments for Atopic Dermatitis: An Update

Systematic Review

February 2022

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Executive Summary

Background

Atopic dermatitis is a chronic inflammatory skin disease characterized by intense itching and recurrent eczematous lesions with a relapsing and remitting pattern. Atopic dermatitis affects roughly 7% of adults and 10% of children in the US. The causes of atopic dermatitis are multifactorial, including environmental, genetic, and immunological components, resulting in disruption in the typical structure and function of the epidermis.

Initial treatment approaches include counseling patients to avoid triggering factors that may initiate or exacerbate symptoms, maintaining the skin barrier integrity through moisturizers, and using topic antiinflammatory therapies such as corticosteroids. More persistent cases may require additional step-up therapy including phototherapy, topical calcineurin inhibitors such as tacrolimus and pimecrolimus, or systemic treatments such as azathioprine, cyclosporine, methotrexate, and mycophenolate. Systemic corticosteroids such as prednisone should only be used for short-term treatment.

Newer therapies for atopic dermatitis include crisaborole (Eucrisa) and dupilumab (Dupixent). The topical Janus kinase inhibitor ruxolitinib (Opzelura) was approved by the US Food and Drug Administration (FDA) for atopic dermatitis in September 2021, and the interleukin-13 antagonist lebrikizumab (Adbry) was approved in December 2021. The oral Janus kinase inhibitors abrocitinib and upadacitinib were approved in January 2022.

Additional therapies currently under investigation include another oral Janus kinase inhibitor (baricitinib) and injectable interleukin-13 antagonists (nemolizumab, tradipitant). Several of these agents were expected to have FDA approval decisions in late 2021, but have been postponed until 2022. Drug Effectiveness Review Project (DERP) participants are interested in updating their 2017 review to better understand the effectiveness and harms of newer medications to treat atopic dermatitis, and the potential of investigational agents that might be approved by the FDA in the near future.

PICOS and Key Questions

This updated review evaluates randomized controlled trials (RCTs) in adults and children (all ages, including infants) with moderate-to-severe atopic dermatitis (eczema), using FDA-approved agents and investigational therapies. For all agents, comparators were another included intervention, topical corticosteroids, and standard of care. For pipeline therapies, placebo-controlled studies were also included. Outcomes included relevant clinical assessments such as Scoring Atopic Dermatitis (SCORAD), Eczema Area and Severity Index (EASI), the Investigators Global Assessment (IGA), and quality of life (QoL) assessments such as the Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (CDLQI). Adverse events (AEs) and serious adverse events (SAEs) were also reported. The Key Questions ask about efficacy and safety of these therapies and about ongoing studies on the topic.

Interventions

Table I. List of Brand Name and Generic Therapies for Atopic Dermatitis

Generic Name	Brand Name	Drug Class	Administration Route	FDA Approval Date
Abrocitinib (PF-04965842)	Cibinqo	JAK inhibitor	Oral	January 2022
Azathioprine	Imuran	Immunosuppressant	Oral	March 1968
Crisaborole	Eucrisa	Phosphodiesterase 4 inhibitor	Topical (ointment)	December 2016
Cyclosporine	Neoral	Immunosuppressant	Oral	July 1995
Dupilumab	Dupixent	IL-4 receptor alpha antagonist	Injection	March 2017
Mycophenolate	Myfortic	Immunosuppressant	Oral	February 2004
Omalizumab	Xolair	Monoclonal antibody	Injection	June 2003
Pimecrolimus	Elidel	Calcineurin inhibitor immunosuppressant	Topical (cream)	December 2001
Ruxolitinib	Opzelura	JAK inhibitor	Topical (cream)	September 2021
Tacrolimus	Protopic	Calcineurin inhibitor immunosuppressant	Topical (ointment)	December 2000
Tralokinumab	Adbry	IL-13 antagonist	Injection	December 2021
Upadacitinib	Rinvoq	JAK inhibitor	Oral	January 2022
Pipeline therapies				
Baricitinib	Olumiant	JAK inhibitor	Oral	NA
Lebrikizumab	NA	IL-13 antagonist	Injection	NA
Nemolizumab	NA	IL-13 antagonist	Injection	NA
Tradipitant (VLY-686)	NA	Neurokinin-1 receptor antagonist	Oral	NA

Abbreviations. IL: interleukin; JAK: Janus kinase; NA: not applicable.

Methods

This review is an update to a previous DERP systematic review and meta-analysis performed in 2017. We followed standard DERP procedures for performing systematic reviews. We searched Ovid MEDLINE, the Cochrane Library, Google Scholar, and other evidence sources up to August 25, 2021 for therapies not covered in the previous DERP review. For those therapies in the previous review, we searched evidence sources from January 1, 2017 to August 25, 2021. We identified ongoing studies through ClinialTrials.gov, the International Standard Randomized Controlled Trials Number (ISRCTN) registry, and the FDA. We selected studies for inclusion if they met our inclusion criteria outlined in the PICOS section. Systematic reviews were not included in this report, but the reference lists contained in these reviews were used to identify additional studies. Risk of bias assessment was conducted on all eligible studies that were published in full-text articles. We also used the Grading of Recommendations, Assessment,

Development, and Evaluation (GRADE) approach to evaluate the certainty of evidence (CoE) for critical outcomes (i.e., SCORAD, EASI, DLQI/CDLQI, IGA, and AEs) reported in full-text articles.

Key Findings

FDA-Approved Therapies

Abrocitinib

- We identified 5 studies, 4 with a *low* risk of bias (RoB) and 1 with a *moderate* RoB.
  - 4 studies compared abrocitinib with placebo and 1 study compared abrocitinib with dupilumab.
  - Studies were relatively large with sample sizes from 267 to 838 participants.
  - A larger proportion of participants treated with abrocitinib achieved an IGA response and EASI-75 (75% reduction in EASI), compared to placebo. We rated this as *high* CoE.
  - Abrocitinib was superior to dupilumab in achieving the goal IGA response and EASI-75 at week 16. This evidence was rated as low CoE.
  - One notable AE associated with abrocitinib is a transient drop in platelets during the first few weeks of treatment.

Azathioprine

- We identified 3 studies in 4 publications evaluating azathioprine in atopic dermatitis with all 3 RCTs rated as having a *moderate* RoB.
  - 2 studies compared azathioprine with placebo for 12 weeks and 1 study compared azathioprine with methotrexate for 12 weeks; this head-to-head study also had a 5-year extension period.
  - Azathioprine improved Six-Area Six-Sign Atopic Dermatitis (SASSAD) severity scores compared with placebo in relatively small studies of 37 and 61 participants.
  - Azathioprine was equally as efficacious as methotrexate over 12 weeks for SCORAD and IGA assessments, with a *moderate* CoE.
    - Few participants (n = 8) continued on their initially assigned therapy in the 5-year follow-up comparing azathioprine and methotrexate.
  - Azathioprine had more reported AEs than placebo over 12 weeks, with gastrointestinal effects more commonly noted.

Crisaborole

- There were no new eligible studies identified for crisaborole for this review. Studies evaluated in the previous DERP review assessed participants with mild-to-moderate disease, which were out of the scope of this review.

Cyclosporine

- We identified 9 eligible RCTs in 10 publications evaluating the efficacy and safety of cyclosporine compared with different comparator groups: 7 of them rated having as *high* RoB, and 2 rated as *moderate* RoB. All of these studies had small sample sizes under 100.
  - The RCT comparing cyclosporine with methotrexate in adults was rated as having a *high* RoB and found that cyclosporine was better than methotrexate.
  - The RCT that compared cyclosporine with methotrexate in pediatric population was rated as having a *moderate* RoB and there was no difference between the 2 groups.

- 1 *high* RoB RCT that compared cyclosporine with EC-MPS studied the participants for 48 weeks and found no differences between the treatment groups.
- 1 RCT evaluated the efficacy and safety of cyclosporine in comparison to prednisolone was rated as having a *high* RoB. Similar efficacy was observed for both treatments in this study.
- Another *moderate* RoB RCT compared cyclosporine with tacrolimus, analyzed the mean differences in SCORAD score, reporting that the primary outcome favored tacrolimus over cyclosporine.
- 3 RCTs favored cyclosporine over placebo, but all were rated as having a *high* RoB.
- Regardless of the comparator group, participants in the cyclosporine group reported more AEs.

Dupilumab

- We did not identify any eligible studies comparing dupilumab to an agent that was FDA-approved at the start of the review. We identified 2 studies comparing dupilumab to agents approved as the review was ongoing (abrocitinib and upadacitinib); these are covered in their respective sections.

Omalizumab

- We identified 1 eligible RCT comparing omalizumab to placebo in pediatric participants with severe atopic dermatitis, and rated as having a *low* RoB.
  - This study evaluated 62 participants for a 24-week treatment period with an additional 24-week follow-up.
  - The primary efficacy outcome of change in SCORAD score at 24 weeks was significantly improved in the omalizumab group, although it fell short of achieving a minimal clinically important difference (MCID) defined by investigators. This evidence was rated as *high* CoE.
  - QoL, as measured by the CDLQI, was significantly improved in the omalizumab group and did achieve the MCID defined by investigators.
  - Respiratory and gastrointestinal AEs were most commonly reported in the omalizumab treatment group.

Pimecrolimus

- We identified 1 *moderate*-RoB RCT evaluating the efficacy and safety of pimecrolimus compared with topical corticosteroids for 5 years in infants with mild-to-moderate disease.
  - Both groups reported rapid improvement in symptoms with nearly half of participants in both treatment arms reporting treatment success defined as an IGA of 0 or 1 by week 3.
  - At the end of the 5-year follow-up nearly 90% of all treated participants in both groups achieved treatment success.
  - By the end of the study period participants assigned pimecrolimus cream used the product a median of 224 days while participants assigned to topical corticosteroids used the product a median of 178 days.
  - High incidences of AEs with over 95% of both groups reporting any event by the end of the study period.

Ruxolitinib

- We identified 2 RCTs in 3 publications; 1 RCT with a *low* RoB and 1 with a *moderate* RoB.
  - Sample sizes were relatively large with 307 to 1,251 participants and study lengths were relatively short at 8 weeks.
  - Participants noted improvement in EASI from baseline with ruxolitinib compared with placebo.
  - Participants on ruxolitinib were 6 times more likely to achieve an IGA of 0 or 1 on treatment compared with placebo.
  - The CoE was mostly *high* for clinical outcomes.
  - Application-site pain were the most commonly reported AEs but were similar to placebo in incidence.

Tacrolimus

- We did not identify any new eligible studies for tacrolimus. In the previous DERP review, there were no significant differences between tacrolimus and pimecrolimus in participants with moderate-to-severe disease.

Tralokinumab

- We identified 4 RCTs in 4 publications with 3 RCTs rated as having a *low* RoB, 1 RCT rated as having a *moderate* RoB, and 1 post hoc analysis.
  - Study periods were up to 52 weeks and included 2,180 unique participants across all phases.
  - Symptoms were reduced from baseline consistently across trials for higher doses, with an overall *low* to *moderate* CoE.
  - QoL was improved while taking tralokinumab with an overall *moderate* CoE.
  - AEs were mild to moderate and occurred similarly to placebo.

Upadacitinib

- We identified 4 RCTs in 4 publications, 3 comparing upadacitinib with placebo and 1 comparing upadacitinib with dupilumab. We rated these studies as having a *low* or *moderate* RoB.
  - Study periods were up to 16 weeks in length vs. placebo and 24 weeks vs. dupilumab, with a total of 3,443 unique adolescents and adults.
  - Symptoms showed significant improvement in upadacitinib participants compared with placebo participants according to EASI assessments.
  - Upadacitinib was superior to dupilumab in achieving an EASI-75 at weeks at 71% vs. 61%. This evidence was rated as *high* CoE.
  - Notable AEs in participants treated with upadacitinib included infections and lymphopenia.

Pipeline Therapies

Baricitinib

- We identified 6 RCTs in 7 publications, all comparing baricitinib with placebo. We rated these studies as having a *low* to *moderate* RoB.
  - Symptoms were significantly improved over placebo according to the SCORAD, EASI, and IGA assessments; we rated these outcomes as a *high* CoE.
  - Study periods were up to 16 weeks in length except for the long-term extension study, which was 68 weeks in length and included 2,132 unique participant across all phases.
  - Discontinuation rates and AEs were similar between baricitinib and placebo over initial treatment study periods.

Lebrikizumab

- We identified 2 RCTs in publications with 1 RCT rated as having a *low* RoB, and 1 RCT as having a *moderate* RoB.
  - Study periods were up to 16 weeks and included 489 unique participants across all phases.
  - Symptoms were reduced from baseline in higher doses with an overall *low* to *moderate* CoE as assessed by SCORAD and EASI.
  - QoL was not consistently improved while taking lebrikizumab with a *very low* CoE.
  - AEs such as injection site reaction were mild to moderate and occurred similarly to placebo.

Nemolizumab

- We identified 3 total RCTs in 6 publications with 2 RCTs rated as having a *low* RoB, 1 RCT rated as having a *moderate* RoB, 1 extension study, and 2 post hoc analyses.
  - Study periods were up to 52 weeks and included 705 unique participants across all phases.
  - Symptoms were reduced from baseline in medium potency doses with an overall *very low* CoE.
  - QoL was improved while taking nemolizumab with an overall *low* CoE.
  - AEs such as injection site reaction were mild to moderate and occurred similarly to placebo.

Tradipitant

- We did not identify any eligible studies for tradipitant.

Discussion

Current therapies for atopic dermatitis include a variety of pharmaceutical agents and treatment modalities, including orally administered products, topical creams, and subcutaneous injections. Older therapies such as azathioprine and cyclosporine are effective, but carry the risks of significant side effects (e.g., systemic immunosuppression). Newer treatment options, such as crisaborole and dupilumab, are effective and improve burden of disease and QoL. Tacrolimus and pimecrolimus have also demonstrated efficacy in previous DERP reviews with no notable differences in efficacy between the agents.

A newer topical FDA-approved treatment for atopic dermatitis is ruxolitinib, which showed good efficacy with high rates of response as assessed by EASI and IGA, as demonstrated in large studies with *high* CoE.

Abrocitinib, baricitinib, and upadacitinib are oral Janus kinase inhibitors for treatment of atopic dermatitis. Abrocitinib and baricitinib generally had similar response rates as assessed by EASI-75, with 29% to 40% of participants achieving goal by week 12 or week 16. Upadacitinib demonstrated higher response rates with 60% to 70% of participants achieving EASI-75. Baricitinib and upadacitinib are already FDA-approved for treatment of rheumatoid arthritis.

Lebrikizumab, nemolizumab, and tralokinumab are injectable monoclonal antibodies that target key drivers of underlining inflammation. Recently FDA-approved lebrikizumab improves efficacy measures (e.g., EASI, IGA) when compared to placebo; however, the effect size is small and phase 3 studies need to be completed to show the true benefit of lebrikizumab. For nemolizumab, completed studies show inconsistent results in efficacy and quality measures among different doses. A moderate dose of nemolizumab demonstrated greater efficacy and fewer AEs compared to higher doses. Nemolizumab appears to be a safe and effective alternative for patients who find no benefit with topical therapies. Tralokinumab was shown to be superior to placebo in both efficacy and quality measures when used for short durations. Demonstrated efficacy with long-term use is inconsistent and further studies are needed to determine the efficacy over 24 weeks of use. Tralokinumab appears to be safe with AEs similar to placebo.

Background

Atopic dermatitis is a chronic inflammatory skin disease characterized by intense itching and recurrent eczematous lesions with a relapsing and remitting pattern.[1] Atopic dermatitis affects roughly 7% of adults and 10% of children in the US.[2] The causes of atopic dermatitis are multifactorial, including environmental, genetic, and immunological components, resulting in disruption in the typical structure and function of the epidermis.[3] The epidermis plays a crucial role for the body in acting as a barrier, and defects in the epidermal layer of the skin are the most significant impacts for those with atopic dermatitis. Atopic dermatitis typically develops within the first 5 years of life, with 85% of cases occurring before the age of 5; however, adult onset still occurs.[4] Children with atopic dermatitis are more likely to be bullied, while adults report atopic dermatitis impairing their social life and affecting their choice of clothing when they go out.[5] Adults and children report atopic dermatitis as negatively affecting their self-esteem, as well as limiting social interaction to avoid discussing their condition.[5] Women are more likely than men to develop this condition, but men tend to have more persistent symptoms, especially later in life.[2,4]

Various proteins are responsible for correct functioning of the epidermal layer, including filaggrin, transglutaminases, keratins, and intracellular proteins.[6] Defects in these proteins, specifically filaggrin, can cause both allergen and microbial penetration into the skin, causing disease exacerbations.[6] Allergens able to penetrate the skin and cause an exacerbation include pollens, foods, and dust mite particles.[6] Atopic skin also has reduced antimicrobial peptides (AMPs), which normally act as a chemical barrier on the skin. Reduced AMPs lead to easier access for bacteria to colonize, correlating with increased susceptibility to infections in these patients.[6] Though skin barrier dysfunction has been considered the first and most significant step in the development of atopic dermatitis, immune dysregulation, including the activation of type 2 immune responses, also results in impairment of the epidermal layer.[6] An elevated type 2 immune response is reflected in an increased frequency of allergen-specific T-cells producing interleukin (IL)-4, -5, and -13, and a decrease in interferon-γ-producing T-cells, in patients with atopic dermatitis.[7] Recently, new insights into the pathophysiology have included abnormalities in the epidermal lipid layer as well as neuroimmune interactions and microbial dysbiosis. This information is being used to guide the development of novel therapeutic and preventative strategies.[6]

Initial treatment approaches include counseling patients to avoid triggering factors that may initiate or exacerbate symptoms, maintain the skin barrier integrity through moisturizers, and using topic antiinflammatory therapies such as corticosteroids.[1] More persistent cases can require additional step-up therapy including phototherapy, topical calcineurin inhibitors such as tacrolimus and pimecrolimus, or systemic treatments such as azathioprine, cyclosporine, methotrexate, and mycophenolate.[1] Systemic corticosteroids such as prednisone should only be used for short-term treatment.[1]

Newer therapies for atopic dermatitis include crisaborole (Eucrisa) and dupilumab (Dupixent). Crisaborole is a phosphodiesterase 4 (PDE4) inhibitor applied topically and considered steroid-sparing.[3] Dupilumab is an injectable monoclonal antibody that decreases the inflammatory response in the skin barrier by blocking IL-4 and IL-13.[8] More recently, the topical Janus kinase (JAK) inhibitor ruxolitinib (Opzelura) was approved for atopic dermatitis by the US Food and

Drug Administration (FDA) in September 2021, while the injectable IL-13 antagonist lebrikizumab (Adbry) was approved in December 2021.[9,10]

Additional therapies currently under investigation include additional JAK inhibitors (upadacitinib, abrocitinib, baricitinib; all oral administration), and injectable IL-13 antagonists (tradipitant, nemolizumab).[1,11]

Drug Effectiveness Review Project (DERP) participants are interested in an update to their 2017 review to understand better the effectiveness and harms of newer medications to treat atopic dermatitis, and the potential of investigational agents that might be approved by the FDA in the near future.

PICOS

Population

- Adults and children (all ages, including infants) with moderate to severe atopic dermatitis (eczema)

Interventions

Table 1. List of Brand Name and Generic Therapies for Atopic Dermatitis

Generic Name	Brand Name	Drug Class	Administration Route	FDA Approval Date
Abrocitinib (PF-04965842)	Cibinqo	JAK inhibitor	Oral	January 2022
Azathioprine	Imuran	Immunosuppressant	Oral	March 1968
Crisaborole	Eucrisa	Phosphodiesterase 4 (PDE4) inhibitor	Topical (ointment)	December 2016
Cyclosporine	Neoral	Immunosuppressant	Oral	July 1995
Dupilumab	Dupixent	IL-4 receptor alpha antagonist	Injection	March 2017
Mycophenolate	Myfortic	Immunosuppressant	Oral	February 2004
Omalizumab	Xolair	Monoclonal antibody	Injection	June 2003
Pimecrolimus	Elidel	Calcineurin inhibitor immunosuppressant	Topical (cream)	December 2001
Ruxolitinib	Opzelura	JAK inhibitor	Topical (cream)	September 2021
Tacrolimus	Protopic	Calcineurin inhibitor immunosuppressant	Topical (ointment)	December 2000
Tralokinumab	Adbry	IL-13 antagonist	Injection	December 2021
Upadacitinib	Rinvoq	JAK inhibitor	Oral	January 2022
Pipeline therapies				
Baricitinib	Olumiant	JAK inhibitor	Oral	NA
Lebrikizumab	NA	IL-13 antagonist	Injection	NA
Nemolizumab	NA	IL-13 antagonist	Injection	NA

Generic Name	Brand Name	Drug Class	Administration Route	FDA Approval Date
Tradipitant (VLY-686)	NA	Neurokinin-1 receptor antagonist	Oral	NA

Abbreviations. IL: interleukin; JAK: Janus kinase; NA: not applicable.

Comparators

- Another included intervention type (head-to-head)
- Topical corticosteroids
- Standard of care or placebo (for pipeline therapies only)

Outcomes

- Response to treatment (e.g., Investigator's Global Assessment)
- Disease symptoms (e.g., Eczema Area and Severity Index score, Peak Pruritus Numerical Rating Scale, Scoring Atopic Dermatitis, percentage of body surface area affected)
- Quality of life (QoL)
- Adverse events (AEs)
- Serious adverse events (SAEs)

Study Designs

- Randomized controlled trials (RCTs)

Key Questions

KQ1. For adults and children, what is the comparative effectiveness of the included interventions for atopic dermatitis?

KQ1. For adults and children, what is the effectiveness of included pipeline therapies for atopic dermatitis?

KQ2. For adults and children, what are the comparative harms of the included interventions for atopic dermatitis?

KQ3. For adults and children, what are the harms of included pipeline therapies for atopic dermatitis?

KQ4. What are the characteristics of ongoing studies for included interventions to treat atopic dermatitis?

Methods

Researchers from the Center for Evidence-based Policy (Center) followed standard DERP procedures for performing systematic reviews. We searched Ovid MEDLINE, the Cochrane Library, Google Scholar, and other evidence sources up to August 25, 2021 for therapies not covered in the previous DERP review. For those therapies included in the previous review, we searched evidence sources from January 1, 2017 to August 25, 2021. We identified ongoing studies were identified through ClinialTrials.gov, the International Standard Randomized Controlled Trials Number (ISRCTN) registry, and the FDA. We included studies if they met our inclusion criteria outlined in the PICOS section. Systematic reviews were not included in this

report, but we used the reference lists of those reviews to identify additional studies. Additional eligibility criteria included studies published in English and conducted in human participants. We conducted risk of bias (RoB) assessment on all eligible studies published in full-text articles. We also used the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach to evaluate the certainty of evidence (CoE) for critical outcomes (i.e., Scoring Atopic Dermatitis [SCORAD], Eczema Area and Severity Index [EASI], Dermatology Life Quality Index/Children's Dermatology Life Quality Index [DLQI/CDLQI], Investigators Global Assessment [IGA], and AEs) reported in full-text articles. Our full search strategy and methods are provided in Appendix A.

Findings

Figure 1 shows the literature flow through the review and the associated PRISMA (preferred reporting items for systematics reviews and meta-analyses) characteristics.

Figure 1. PRISMA Diagram

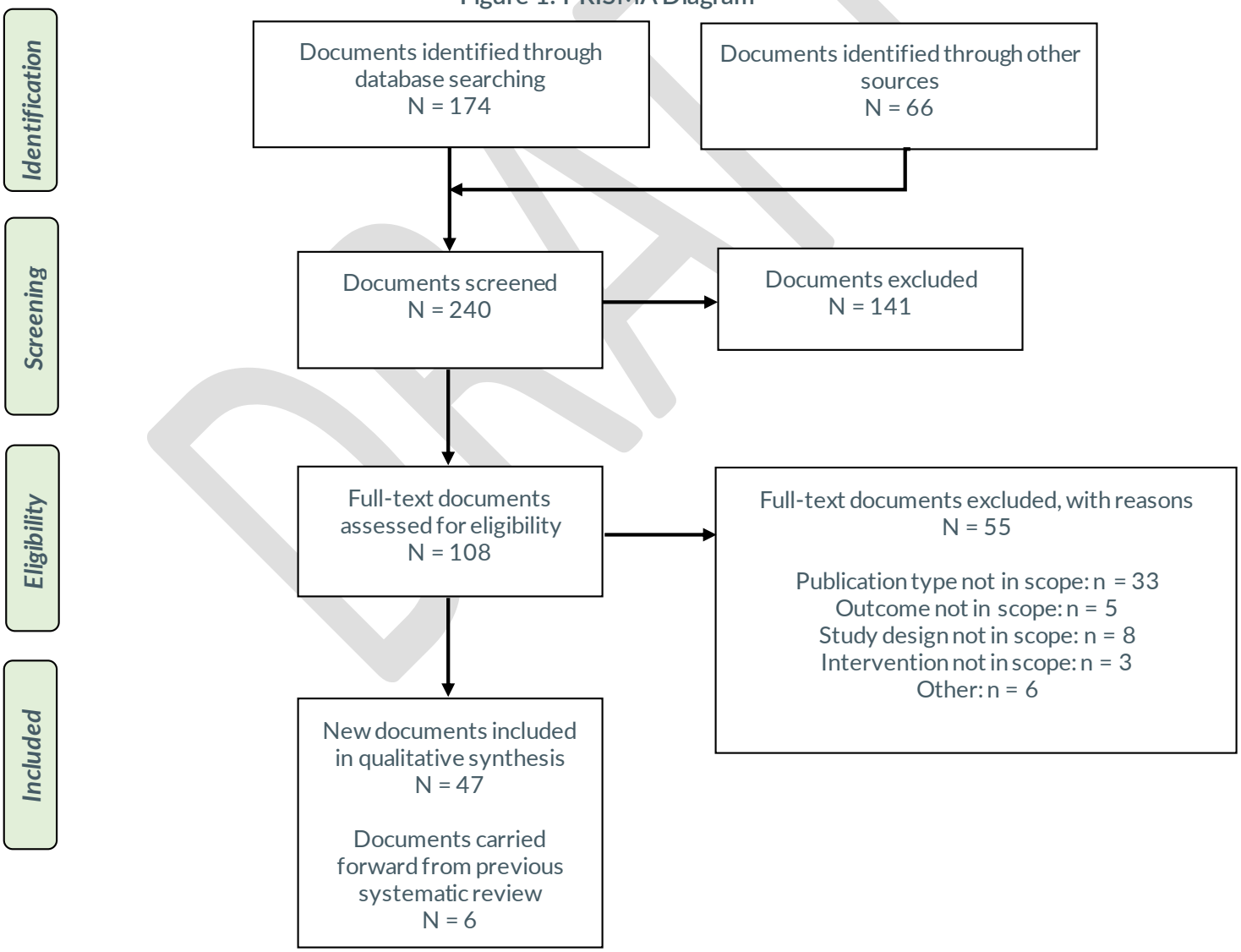

Table 2 provides a summary of findings and GRADE ratings for relevant clinical outcomes for the interventions listed in this review.

Table 2. Summary of Findings (GRADE) for Atopic Dermatitis

Number of Studies Sample Size	Treatment Groups Quality of Evidence	Relationship	Rationale
SCORing Atopic Dermatitis (SCORAD)			
4 RCTs[12-15] N = 1,318	Abrocitinib vs. placebo High	Abrocitinib was superior to placebo	Not downgraded
1 RCT[16] N = 838	Abrocitinib vs. dupilumab vs. placebo Moderate	Abrocitinib was superior to placebo Abrocitinib was equally as efficacious as dupilumab	Downgraded 1 level for indirectness
1 RCT[17] N = 42	Azathioprine vs. methotrexate Low	Azathioprine was equally as efficacious as methotrexate	Downgraded 1 level each for imprecision and indirectness
4 RCTs[18-21] N = 2,132	Baricitinib vs. placebo High	Baricitinib was superior to placebo	Not downgraded
2 RCTs[22,23] N = 137	Cyclosporine vs. methotrexate: Very low	Unclear relationship between cyclosporine and methotrexate	Downgraded 2 levels for risk of bias and 1 level for indirectness
1 RCT[24] N = 50	Cyclosporine vs. EC-MPS Very Low	EC-MPS was similar to cyclosporine	Downgraded 2 levels for risk of bias and 1 level for imprecision
1 RCT[25] N = 38	Cyclosporine vs. prednisolone Very Low	Prednisolone had similar efficacy to cyclosporine	Downgraded 2 levels for risk of bias and 1 level for imprecision
1 RCT[26] N = 30	Cyclosporine vs. tacrolimus Very Low	Tacrolimus was superior to cyclosporine	Downgraded 1 level each for risk of bias, inconsistency, imprecision
1 RCTs[27] N = 209	Lebrikizumab vs. placebo Low	Lebrikizumab showed superiority over placebo	Downgraded 1 level each for inconsistency and imprecision
2 RCTs[28,29] N = 490 1 NRS[30] N = 191	Nemolizumab vs. placebo Very low	Nemolizumab has a dose dependent superiority to placebo with lower doses showing more benefit	Downgraded 1 level each for inconsistency, indirectness, and imprecision
1 RCT[31] N = 65	Omalizumab vs. placebo Low	Omalizumab was superior to placebo	Downgraded 1 level each for imprecision and indirectness
4 RCTs[32-35] N = 2,180	Tralokinumab vs. placebo Moderate	Tralokinumab showed superiority over placebo	Downgraded 1 level for indirectness

Number of Studies Sample Size	Treatment Groups Quality of Evidence	Relationship	Rationale
Eczema Activity and Severity Index (EASI)			
4 RCTs[12-15] N = 1,318	Abrocitinib vs. placebo High	Abrocitinib was superior to placebo	Not downgraded
1 RCT[16] N = 838	Abrocitinib vs. dupilumab vs. placebo Moderate	Abrocitinib was superior to placebo Abrocitinib was equally as efficacious as dupilumab	Downgraded 1 level for indirectness
1 RCT[17] N = 42	Azathioprine vs. methotrexate Low	Azathioprine was equally as efficacious as methotrexate	Downgraded 1 level each for imprecision and indirectness
4 RCTs[18-21] N = 2,132	Baricitinib vs. placebo High	Baricitinib was superior to placebo	Not downgraded
1 RCT[23] N = 97	Cyclosporine vs. methotrexate Very Low	Higher doses of methotrexate had similar efficacy to cyclosporine	Downgraded 2 levels for risk of bias and 1 level for imprecision
2 RCTs[27,36] N = 489	Lebrikizumab vs. placebo Moderate	Lebrikizumab showed dose dependent improvements over placebo	Downgraded 1 level for imprecision
3 RCTs[28,29,37] N = 705 1 NRS[30] N = 191	Nemolizumab vs. placebo Very Low	Nemolizumab has a dose dependent superiority to placebo	Downgraded 1 level each for inconsistency, indirectness, and imprecision
1 RCT[31] N = 65	Omalizumab vs. placebo Low	Omalizumab was superior to placebo	Downgraded 1 level each for imprecision and indirectness
2 RCTs[38,39] N = 1,556	Ruxolitinib vs. placebo High	Ruxolitinib was superior to placebo	Not downgraded
4 RCTs[32-35] N = 2,180	Tralokinumab vs. placebo Moderate	Tralokinumab showed superiority over placebo	Downgraded 1 level for inconsistency
3 RCTs[40-42] N = 1,850	Upadacitinib vs. placebo High	Upadacitinib was superior to placebo	Not downgraded
1 RCT[43] N = 692	Upadacitinib vs. dupilumab High	Upadacitinib was superior to dupilumab	Downgraded 1 for indirectness
Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (CDLQI)			
3 RCT[12,14,15] N = 1,051	Abrocitinib vs. placebo High	Abrocitinib was superior to placebo	Not downgraded
1 RCT[16] N = 838	Abrocitinib vs. dupilumab vs. placebo Moderate	Abrocitinib was superior to placebo Abrocitinib was equally as efficacious as dupilumab	Downgraded 1 level for indirectness

Number of Studies Sample Size	Treatment Groups Quality of Evidence	Relationship	Rationale
1 RCT[44] N = 61	Azathioprine vs. placebo Low	Azathioprine was superior to placebo	Downgraded 1 level each for imprecision and indirectness
4 RCTs[18,20,21,45] N = 2,132	Baricitinib vs. placebo High	Baricitinib was superior to placebo	Not downgraded
1 RCT[23] N = 97	Cyclosporine vs. methotrexate Very low	Cyclosporine could be superior to methotrexate, but higher doses of methotrexate may achieve similar efficacy in longer terms	Downgraded 2 levels for risk of bias and 1 level for indirectness
1 RCT[24] N = 50	Cyclosporine vs. EC-MPS Very low	Unclear relationship between cyclosporine and EC-MPS	Downgraded 1 level each for risk of bias, imprecision, and inconsistency
1 RCT[25] N = 38	Cyclosporine vs. prednisolone Very low	Cyclosporine was similar to prednisolone	Downgraded 2 levels for risk of bias and 1 level for imprecision
2 RCTs[27,36] N = 489	Lebrikizumab vs. placebo Very low	Lebrikizumab showed mixed results when compared to placebo	Downgraded 1 level each for inconsistency, indirectness, and imprecision
3 RCTs[28,29,37] N = 705 1 NRS[30] N = 191	Nemolizumab vs. placebo Low	Nemolizumab significantly improved over placebo	Downgraded 1 level each for inconsistency and indirectness
1 RCT[31] N = 65	Omalizumab vs. placebo Low	Omalizumab was superior to placebo	Downgraded 1 level each for imprecision and indirectness
4 RCTs[32-35] N = 2,180	Tralokinumab vs. placebo Moderate	Tralokinumab showed superiority over placebo at higher doses	Downgraded 1 indirectness
3 RCTs[40-42] N = 1,850	Upadacitinib vs. placebo High	Upadacitinib was superior to placebo	Not downgraded
Investigator Global Assessment (IGA)			
4 RCT[12-15] N = 1,318	Abrocitinib vs. placebo High	Abrocitinib was superior to placebo	Not downgraded
1 RCT[16] N = 838	Abrocitinib vs. dupilumab vs. placebo Moderate	Abrocitinib was superior to placebo Abrocitinib was equally as efficacious as dupilumab	Downgraded 1 level for indirectness
1 RCT[17] N = 42	Azathioprine vs. methotrexate Low	Azathioprine was equally as efficacious as methotrexate	Downgraded 1 level each for imprecision and indirectness

Number of Studies Sample Size	Treatment Groups Quality of Evidence	Relationship	Rationale
4 RCTs[19-21,46] N = 2,132	Baricitinib vs. placebo High	Baricitinib was superior to placebo	Not downgraded
1 RCT[25] N = 38	Cyclosporine vs. prednisolone Very low	Cyclosporine was similar to prednisolone	Downgraded 2 levels for risk of bias and 1 level for imprecision
2 RCTs[27,36] N = 489	Lebrikizumab vs. placebo Low	Lebrikizumab showed a dose dependent improvement over placebo	Downgraded 1 level each for indirectness and imprecision
2 RCTs[28,29] N = 490 1 NRS[30] N = 191	Nemolizumab vs. placebo Very low	Nemolizumab has a dose dependent superiority to placebo	Downgraded 1 level each for inconsistency, indirectness, and imprecision
1 RCT[47] N = 2,418	Pimecrolimus vs. TCS Moderate	Pimecrolimus was superior to placebo	Downgraded 1 level for indirectness
4 RCTs[32-35] N = 2,180	Tralokinumab vs. placebo Low	Tralokinumab showed superiority over placebo	Downgraded 1 level each for inconsistency and indirectness
3 RCTs[40-42] N = 2,751	Upadacitinib vs. placebo High	Upadacitinib was superior to placebo	Not downgraded
Adverse events (AEs)			
4 RCTs[12-15] N = 1,318	Abrocitinib vs. placebo High	Abrocitinib had similar AEs to placebo with a higher rates of GI disorders, acne, herpes and thrombocytopenia	Not downgraded
1 RCT[16] N = 838	Abrocitinib vs. dupilumab vs. placebo Moderate	Abrocitinib had similar AEs to placebo and dupilumab with higher rates of acne, nausea, and herpes Dupilumab had higher conjunctivitis	Downgraded 1 level for indirectness
3 RCTs[17,44,48] N = 140	Azathioprine vs. methotrexate Moderate	Azathioprine had similar AEs to methotrexate with higher rates of blood abnormalities	Downgraded 1 level for inconsistency
4 RCTs[18-21] N = 2,132	Baricitinib vs. placebo High	Baricitinib had similar AEs to placebo with higher rates of headache, increased CPK, infections	Not downgraded
2 RCTs[22,23] N = 137	Cyclosporine vs. methotrexate Very low	Methotrexate may have a better safety profile than cyclosporine	Downgraded 2 levels for risk of bias and 1 level for indirectness

Number of Studies Sample Size	Treatment Groups Quality of Evidence	Relationship	Rationale
1 RCT[24] N = 50	Cyclosporine vs. EC-MPS Very Low	EC-MPS may have a favorable safety profile than cyclosporine	Downgraded 2 levels for risk of bias and 1 level for imprecision
1 RCT[25] N = 38	Cyclosporine vs. prednisolone Very low	Unclear relationship between cyclosporine and prednisolone	Downgraded 2 levels for risk of bias, 1 level for imprecision, and 1 level for indirectness
1 RCT[26] N = 30	Cyclosporine vs. tacrolimus Very Low	Cyclosporine and tacrolimus had similar safety profiles.	Downgraded 1 level each for risk of bias, imprecision and indirectness
3 RCTs (4 publications)[49-52] N = 103	Cyclosporine vs. placebo Very Low	Cyclosporine had worse safety profile than placebo	Downgraded 2 levels for risk of bias and 1 level for imprecision
2 RCTs[27,36] N = 489	Lebrikizumab vs. placebo Low	Lebrikizumab showed similar adverse effects to placebo	Downgraded 1 level each for inconsistency and indirectness
3 RCTs[28,29,37] N = 705 1 NRS[30] N = 191	Nemolizumab vs. placebo Moderate	Slight increased risk over placebo for mild to moderate AEs	Downgraded 1 level for indirectness
1 RCT[31] N = 65	Omalizumab vs. placebo Low	Omalizumab was similar to placebo	Downgraded 1 level each for imprecision indirectness
1 RCT[47] N = 2,418	Pimecrolimus vs. TCS Moderate	Pimecrolimus was superior to placebo	Downgraded 1 level for indirectness
2 RCTs[39,53] N = 1,556	Ruxolitinib vs. placebo High	Ruxolitinib was similar to vehicle placebo	Not downgraded
4 RCTs[32-35] N = 2,180	Tralokinumab vs. placebo Low	Tralokinumab is well-tolerated and increases risk for infection-type AEs over placebo	Downgraded 1 level each for inconsistency and indirectness
3 RCTs[40-42] N = 2,751	Upadacitinib vs. placebo High	Upadacitinib had similar AEs to placebo with higher rates of acne	Not downgraded
1 RCT[43] N = 692	Upadacitinib vs. dupilumab Moderate	Upadacitinib had similar AEs to dupilumab with higher rates of acne, URTI, increased CPK	Downgraded 1 level for indirectness

Abbreviations. AE: adverse event; CPK: creatinine phosphokinase; EC-MPS: enteric coated mycophenolate sodium; GI: gastrointestinal; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; NRS: nonrandomized study; RCT: randomized controlled trial; TCS: topical corticosteroid; URTI: upper respiratory tract infection.

Overview of Assessment Scales

Numerous assessments are performed on individuals with atopic dermatitis, documenting severity and course of disease, response to treatment, and QoL. Table 3 provides an overview of common assessment tools referenced throughout this report.

Table 3. Common Assessments for Atopic Dermatitis

Assessment	Description
Dermatology Life Quality Index (DLQI)[54] Children's Dermatology Life Quality Index (CDLQI)[55]	Tools assess 10 questions including impact of atopic dermatitis on itch, embarrassment, clothing, work/school, and relationships. Questions rated on a 0 to 3 scale. Total score can range from 0 to 30; higher scores indicate lower quality of life.
Eczema Area and Severity Index (EASI)[56]	Assesses proportion of skin affected in 4 defined body regions graded on a 0 to 6 scale; severity then rated on a 0 to 3 scale for each of those regions. Total score can range from 0 to 72; higher scores indicate more severe disease.
Eczema Disability Index (EDI)[57]	Assesses 15 questions on 5 dimensions of quality of life on a combined categorical and linear analogue scale from 0 to 6: • Daily activity (5 items) • Work and school (3 items) • Personal relationship (2 items) • Leisure (4 items) • Treatment (1 item) Higher score represents more severe disease.
Investigator Global Assessment (IGA)[58]	A 5-point scale of overall disease activity; higher scores indicate more severe disease.
Patient-Oriented Eczema Measure (POEM)[59]	Assesses 7 questions on frequency and severity of symptoms on a 0 to 4 scale, covering the previous week. Total score can range from 0 to 28; higher scores indicate more severe disease.
Peak Pruritus Numerical Rating Scale (PP-NRS)[60] Itch Numerical Rating Scale[61]	Assesses overall itch severity in the previous 24 hours on a 0 to 10 scale. Higher scores indicate more severe disease.
Pruritus and Symptom Assessment for Atopic Dermatitis (PSAAD)[62]	Assesses 11 symptoms on a 0 to 10 scale daily. Scores on the symptoms are averaged. Total score can range from 0 to 10 with higher scores indicating more severe disease.
Scoring Atopic Dermatitis (SCORAD)[63]	Assesses 6 domains, each graded on a 0 to 3 scale: • Redness • Swelling • Oozing • Scratch marks • Skin thickening • Dryness Additional symptoms graded on a 0 to 10 scale include itching and sleep disturbance. Total score can range from 0 to 103 with higher scores indicating more severe disease.

FDA-Approved Therapies

Abrocitinib

Study Characteristics

We identified 5 *low* RoB studies analyzing the use of abrocitinib for moderate-to-severe atopic dermatitis: 1 phase-2b RCT and 4 phase-3 RCTs.[12-16] A majority of the studies compared abrocitinib with placebo.[12-15] One study compared abrocitinib to dupilumab.[16] Efficacy outcomes included IGA, EASI, Peak Pruritus Numerical Rating Scale (PP-NRS), percent total body surface area (TBSA), SCORAD, Pruritis and Symptoms Assessment for Atopic Dermatitis (PSAAD), Patient-Oriented Eczema Measure (POEM), DLQI, Patient Global Assessment, and Hospital and Anxiety Depression Scale (HADS).[12-16] Harm outcomes included incidence and severity of AEs.[12-16] Two studies included participants 18 years or older, 2 studies included participants 12 years or older with a body mass of at least 40 kg (88 pounds), and 1 study only included participants aged 12 to 17 years who weighed at least 55 pounds.[12-16] All studies confirmed moderate-to-severe atopic dermatitis diagnosis with IGA of 3 or more, EASI score of 16 or more, TBSA of at least 10%, and PP-NRS of 4 or more for at least 6 months to a year before initiation of study.[12-16] Participants were deemed to have had inadequate response to topical corticosteroids (TCS) or topical calcineurin inhibitors administered for 4 weeks or more based on investigators judgement or inability to receive topical treatments within 12 months of the study.[12-16] Participants were only allowed to use oral antihistamine and nonmedicated emollients during the study.[12-16] Table 4 provides an overview of the pertinent study characteristics for abrocitinib.

Table 4. Study Characteristics: Abrocitinib for Atopic Dermatitis

Author, Year Trial Number Trial Name Risk of Bias	Participants	Product, Dose, Frequency	Study Design	Duration
Gooderham et al., 2019[13] NCT02780167 Low	N = 267	Abrocitinib 10 mg daily, n = 49 Abrocitinib 30 mg daily, n = 50 Abrocitinib 100 mg daily, n = 55 Abrocitinib 200 mg daily, n = 54 Placebo daily, n = 55	Randomized double-blind, Phase 2b, placebo-controlled study	12 weeks
Simpson et al., 2020[15] NCT03349060 JADE MONO-1 Low	N = 387	Abrocitinib 100 mg daily, n = 156 Abrocitinib 200 mg daily, n = 154 Placebo daily, n = 77	Randomized, double-blind, phase 3, placebo-controlled study	12 weeks
Silverberg et al., 2020[14] NCT03575871 JADE MONO-2 Low	N = 391	Abrocitinib 100 mg daily, n = 137 Abrocitinib 200 mg daily, n = 141 Placebo daily, n = 52	Randomized, double blind, phase 3, placebo-controlled study	12 weeks

Author, Year Trial Number Trial Name Risk of Bias	Participants	Product, Dose, Frequency	Study Design	Duration
Beiber et al., 2021[16] NCT03720470 JADE COMPARE Low	N = 838	Abrocitinib 100 mg daily, n = 238 Abrocitinib 200 mg daily, n = 226 Dupilumab 300 mg every other week, n = 242 Placebo daily, n = 131	Randomized, double blind, phase 3, placebo controlled, comparative trial	16 weeks
Echenfield et al., 2021[12] NCT03796676 JADE TEEN Low	N = 273	Abrocitinib 100 mg daily, n = 92 Abrocitinib 200 mg daily, n = 91 Placebo daily, n = 90	Randomized, double blind, phase 3, placebo controlled, parallel group trial	12 weeks

Gooderham and colleagues conducted one of the first large, double-blind, phase 2b, dose-finding trials to determine efficacy of once daily abrocitinib in adults (aged 18 to 75) over 12 weeks.[13] For atopic dermatitis diagnosis upon enrollment, the EASI score was lower than other trials (12 or more) and they did not take PP-NRS into account.[13] The study randomized 267 participants to receive abrocitinib 10 mg, 30 mg, 100 mg, 200 mg, or placebo daily.[13] The primary outcome of Gooderham and colleagues was the proportion of participants who achieved IGA of 0 or 1 with an improvement from baseline of at least 2 grades.[13] Secondary outcomes included proportion of participants achieving a 75% reduction in EASI (EASI-75), PP-NRS response, change from baseline in percent TBSA, and percent change from baseline in SCORAD.[13] Photographs of atopic dermatitis lesions were obtained at selected sites on day 1, week 6, and week 12.[13] Safety and tolerability were assessed by monitoring for TEAEs, vital signs, and laboratory tests.[13]

The JADE MONO-1 and JADE MONO-2 studies were double-blind, phase 3 clinical trials in adolescents and adults with moderate-to-severe atopic dermatitis.[14,15] Participants received either once-daily doses of abrocitinib 100 mg, abrocitinib 200 mg, or placebo as monotherapy over 12 weeks. Participants 12 years or older were included if they had a body mass of at least 40 kg, and all participants had to have confirmed diagnosis of atopic dermatitis for at least 1 year prior to randomization or first dose of study drug.[14,15] The primary outcomes included the proportion of participants with IGA score improvement and EASI-75 at week 12.[14,15] Secondary endpoints included IGA and EASI-75 score at other time points, EASI-50, EASI-90, PP-NRS improvement, time to PP-NRS response, mean change in PSAAD, and improvement in SCORAD.[14,15] Participant-reported outcomes included POEM score and DLQI score.[15] JADE MONO-2 also reported POEM score, Patient Global Assessment score, and HADS scores.[14] Safety and tolerability were assessed by monitoring all AEs from first dose to 12 weeks and 28 days after the last dose, clinical abnormalities, laboratory tests, ECG and vital signs.[14,15]

JADE TEEN compared abrocitinib 200 mg, 100 mg, or placebo in combination with topical therapy in participants aged 12 to 17 years with moderate-to-severe atopic dermatitis.[12] Eligible participants had to weigh at least 55 pounds and have a confirmed diagnosis of atopic dermatitis as described above.[12] In this trial, participants were allowed to use nonmedicated and medicated topical therapies as well as oral antihistamines.[12] A total of 273 participants completed the study; 56.1% of these identified as White, 33% as Asian, 26.7% as Hispanic or Latino, and 6% as Black.[12] The primary outcomes were IGA and EASI-75 response. Secondary outcomes includes the proportion of participants who improved in PP-NRS score, EASI-50, EASI-90, EASI-100 SCORAD, PSAAD, CDLQI, POEM, and the Dermatitis Family Impact scale.[12] All incidence of AEs, SAEs, and AEs resulting in discontinuation were recorded and monitored with vital signs, laboratory tests, urinalysis, and lipid panels at different time points (2, 4, 8 and 12 weeks) throughout therapy.[12]

JADE COMPARE was a double-blind, double-dummy, phase 3 RCT that compared abrocitinib 200 mg, abrocitinib 100 mg orally once daily, dupilumab 300 mg subcutaneously every other week, and placebo in adults (≥ 18 years) for 16 weeks.[16] All participants were also allowed to receive topical therapies (once daily) such as low- or medium-potency topical glucocorticoids, topical calcineurin inhibitors, and topical phosphodiesterase 4 inhibitors.[16] Rescue therapy in the form of systemic or topical treatments (low- or medium-potency agents) was not allowed.[16] The primary outcomes of this trial were IGA response and EASI-75 response at week 12.[16] Key secondary outcomes included PP-NRS response at week 2, IGA and EASI-75 response at week 16.[16] Other secondary outcomes assessed were EASI-50, EASI-90, EASI-100, time to itch, change in percent TBSA involvement, POEM, PSAAD, DLQI, HADS, and SCORAD.[16]

Efficacy Outcomes

Abrocitinib demonstrated efficacy over placebo in almost all outcomes.[12-16] In all instances, the abrocitinib 200 mg showed greater efficacy than the abrocitinib 100 mg.[12-16]

Gooderham and colleagues reported a large number of discontinuations in participants receiving abrocitinib 10 mg, 30 mg, and placebo compared to participants on the abrocitinib 100 mg and 200 mg, due to insufficient clinical response and also use of prohibited medications.[13] The percent of participants who achieved IGA of 0 or 1 were 43.8% (21 of 48; $P < .01$) abrocitinib 200 mg, 29.6% (16 of 54; $P < .01$) abrocitinib 100 mg, 8.9% (4 of 45; $P < .56$) abrocitinib 30 mg,[13]10.9% (5 of 46; $P < .36$) abrocitinib 10 mg, and 5.8% (3 of 52) on placebo.[13] Percent reductions from baseline in EASI were 82.6% (90% CI, −92.8 to −72.4; $P < .01$), 59% (90% CI, −69.3 to −48.8; $P < .01$) and 35.2% (90% CI, −46.1 to −24.4) for those receiving abrocitinib 200 mg, abrocitinib 100 mg, and placebo respectively.[13] EASI-75 responders were 64.6% (31 of 48; 90% CI, 4.26 to 21.19) for abrocitinib 200 mg, 40.7% (22 of 54; 90% CI, 1.77 to 8.41) for abrocitinib 100 mg, 13.3% (6 of 45; 90% CI, 0.31 to 2.06) for 30 mg abrocitinib, 17.4% (8 of 46; 90% CI, 0.52 to 3.07) for abrocitinib 10 mg, and 15.4% (8 of 52) for placebo.[13] The PP-NRS score significantly reduced (≥ 4 points for participants with baseline PP-NRS score ≥ 4) in the abrocitinib 200 mg (63.6%; 90% CI, 2.43 to 10.77) and abrocitinib 100 mg groups (50%; 90% CI, 1.40 to 5.76), compared to placebo.[13]

At 12 weeks, the JADE MONO-1 trial demonstrated an IGA response for 44% (67 of 153; 95% confidence interval [CI], 26.2 to 45.7; $P < .01$) in the abrocitinib 200 mg group, 24% (37 of 156;

95% CI, 6.8 to 24.8; *P* < .01) of the 100 mg group, and 8% (6 of 76) of the placebo group.[15] The proportion of participants who had an EASI-75 response were 63% (96 of 156; 95% CI, 40.5 to 61.5; *P* < .01), 40% (62 of 156; 95% CI, 17.4 to 38.3; *P* < .01), and 12% (9 of 76) for abrocitinib 200 mg, abrocitinib 100 mg, and placebo, respectively.[15] The PP-NRS responders at week 12 were 57% (84 of 147; *P* < .01) for the abrocitinib 200 mg, 38% (55 of 147, *P* < .01) for the abrocitinib 100 mg and 15% (11 of 74) for the placebo groups.[15] The reduction in PP-NRS was observed within 1 day of the first treatment dose.[15] For participant-reported outcomes such as the DLQI score, the least squares mean change from baseline was −9.1 (95% CI, −10.3 to −8), −7 (95% CI, −8.1 to −5.8), and −4.2 (95% CI, −5.9 to −2.5) for the abrocitinib 200 mg, abrocitinib 100 mg and placebo, respectively.[15] The CLDQI score was assessed for the adolescents and the least squares mean change was −7.5 (95% CI, −8.9 to −6.0) for abrocitinib 200 mg, −6.4 (95% CI, −7.9 to −5.0) for abrocitinib 100 mg, and −3.9 (95% CI, −6.1 to −1.7) for the placebo.[15] Change in POEM from baseline was −10.6 (95% CI, −11.8 to −9.4) for abrocitinib 200 mg, −6.8 (95% CI, −8.0 to −5.6) for abrocitinib 100 mg, and −3.7 (95% CI, −5.5 to −1.9) for placebo.[15]

The JADE MONO-2 trial demonstrated abrocitinib efficacy at week 12 with 38.1% (59 of 155), 28.4% (44 of 155), and 9.1% (7 of 77) having an IGA response for the 200 mg group, 100 mg group, and placebo group (*P* < .01), respectively.[14] The EASI-75 response at week 12 was 61% (94 of 154), 44.5% (69 or 155), and 10.4% (8 of 77) for the abrocitinib 200 mg group, abrocitinib 100 mg group, and placebo group (*P* < .01), respectively.[14] When both IGA and EASI-75 were analyzed separately for participants younger than 18 years and 18 years and older, the results were similar to the total percentages.[14] Decreases from baseline were observed for both the PSAAD and SCORAD for the abrocitinib 200 mg, (−3.0 [95% CI, −3.3 to −2.7] and −56.2 [95% CI, −61.2 to −51.1]), and abrocitinib 100 mg (−2.4 [95% CI, −2.8 to −2.1] and −45.8 [95% CI, −50.9 to −40.7]), compared to placebo (−0.8 [95% CI, −1.3 to −0.3] and −22.7 [95% CI, −30.4 to −15.1]).[14] Participant-reported outcomes such as the POEM and DLQI both had greater improvements at week 12 in the abrocitinib 200 mg (−9.8; 95% CI, −10.7 to −8.8) and abrocitinib 100 mg (−8.3; 95% CI, −9.3 to −7.3) groups, compared to placebo (−3.9; 95% CI, −5.3 to −2.4) for the DLQI and −11 (95% CI, −12.1 to −9.8) and −8.7 (95% CI, −9.9 to −7.5) versus −3.6 (95% CI, −5.3 to −1.9) for the POEM, respectively.[14]

In the JADE TEEN study efficacy with the abrocitinib 200 mg and 100 mg were demonstrated by increases in proportion of participants with IGA response and EASI-75 response.[12] In the abrocitinib 200 mg, 100 mg, and placebo groups, the proportion of participants with an IGA response at week 12 were 46.2%, 41.6% and 24.5%, respectively.[12] The EASI-75 response rate at week 12 were 72%, 68.5% and 41% for abrocitinib 200 mg, 100 mg and placebo, respectively.[12] Furthermore, the abrocitinib groups of 200 mg and 100 mg achieved higher responses for the EASI-50, EASI-90, PP-NRS, PSAAD and SCORAD compared to placebo.[12] For the participant-reported outcomes of CDLQI, POEM and Dermatitis Family Impact scores, the abrocitinib groups showed improvements in all scores from week 2 to 12 versus placebo.[12]

The JADE COMPARE study found a week-12 IGA response of 48.4% (106 of 219), 36.6% (86 of 235), 36.5% (88 of 241) and 14% (18 of 129) for the abrocitinib 200 mg, abrocitinib 100 mg, dupilumab, and placebo groups, respectively.[16] For the EASI-75, response was seen as 70.3% (154 of 219), 58.7% (138 of 235), 58.1% (140 of 241), and 27.1% (35 of 129) for the abrocitinib 200 mg, abrocitinib 100 mg, dupilumab, and placebo groups, respectively.[16] The reported

weighted differences for the IGA response between abrocitinib 200 mg versus placebo was 34.8% (95% CI, 26.1 to 43.5; *P* < .01) and for the abrocitinib 100 mg versus placebo, it was 23.1% (95% CI, 14.7 to 31.4; *P* < .01).[16] Weighted differences of the EASI-75 responses for abrocitinib 200 mg versus placebo was 43.2% (95% CI, 33.7 to 52.7; *P* < .01) and for abrocitinib 100 mg versus placebo was 31.9% (95% CI, 22.2 to 41.6; *P* < .01).[16] The IGA response at week 16 was 47.5% (105 of 221), 34.8% (80 of 230), 38.8% (90 of 232), and 12.9% (16 of 124) in the abrocitinib 200 mg, abrocitinib 100 mg, dupilumab, and placebo groups, respectively.[16] The weighted difference for the abrocitinib 200 mg group and dupilumab group was 9.4% (95% CI, 0.4 to 18.5), and for the abrocitinib 100 mg group and dupilumab group was −3.5% (95% CI, −12.2 to 5.2).[16] The EASI-75 response at week 16 was 71% (157 of 221), 60.3% (138 of 229), 65.5% (152 of 232) and 30.6% (38 of 124) for the abrocitinib 200 mg, abrocitinib 100 mg, dupilumab, and placebo groups, respectively.

Harm Outcomes

Gooderham and colleagues reported harm outcomes for 184 of 267 (68.9%) participants.[13] Most of the AEs were mild and 24% were considered related to treatment.[13] SAEs were reported by 3.4% of participants and included pneumonia (n = 1; abrocitinib 200 mg), eczema herpeticum (n = 1; abrocitinib 100 mg), herpes simplex (n = 2; 1 placebo, 1 active treatment), and herpes zoster (n = 1; abrocitinib 10 mg).[13] The most frequent treatment-related AEs included diarrhea, nausea, viral upper respiratory tract infection (URTI), headache, and atopic dermatitis.[13] Dose response–related decreases in platelet counts were observed in 2 (0.8%) participants, but were less than $100 \times 10^3/\mu L$. Overall, 16.5% (44 of 267) of participants discontinued treatment because of TEAEs.[13]

In the Simpson and colleagues study, AEs occurred in 69% (108 of 156) of the abrocitinib 100 mg group, 78% (120 of 154) of the abrocitinib 200 mg group, and 57% (44 of 77) of the placebo group.[15] SAEs were reported in 3% (5 of 156) of the abrocitinib 100 mg, 3% (5 of 154) of the abrocitinib 200 mg and 4% (3 of 77) of the placebo groups.[15] The most frequently reported AEs (≥ 5%) were nausea, nasopharyngitis, headache, URTI, and atopic dermatitis.[15] Two SAEs were considered treatment-related: 1 inflammatory bowel disease and 1 pancreatitis.[15] In both cases, abrocitinib was discontinued and the participants recovered.[15] Overall discontinuation occurred in 6% (9 of 156) of the abrocitinib 100 mg, 6% (9 of 154) of the abrocitinib 200 mg, and 9% (7 of 77) of the placebo groups.[15] Herpes simplex, herpes zoster, oral herpes and eczema herpeticum occurred in all groups at 1% to 2%.[15] Dose-related decreases in platelet counts occurred in both abrocitinib groups with a nadir occurring at week 4 and returning to baseline afterwards.[15]

For the JADE MONO-2 trial, treatment discontinuation occurred more in the placebo group compared to the abrocitinib groups, 33.3% (26 of 78) versus 9.0% in the abrocitinib 200 mg (14 of 155) and 13.3% of the abrocitinib 100 mg group (21 of 158), respectively.[14] TEAEs occurred at rates of 65.8%, 62.7% and 53.8% for the abrocitinib 200 mg, 100 mg, and placebo groups, respectively.[14] The most frequently reported TEAEs in the abrocitinib groups were nausea (14.2%; 22 of 155) and nasopharyngitis (12.7%; 20 of 158).[14] The most reported TEAE in the placebo group was atopic dermatitis (15.4%; 12 of 78).[14] Other TEAEs that occurred in at least 3% included headache, URTI, acne, vomiting, upper abdominal pain, increased creatinine phosphokinase (CPK), folliculitis and thrombocytopenia.[14] All participants with thrombocytopenia

had platelet counts return to baseline and no participants discontinued the study due to thrombocytopenia.[14]

In the JADE TEEN study, overall treatment-emergent AEs occurred at 62.8%, 56.8% and 52.1% in the abrocitinib 200 mg, abrocitinib 100 mg, and placebo groups, respectively.[12] Of these 2.1% (n = 2) of participants in the abrocitinib 200 mg group and 2.1% (n = 2) of participants in the placebo groups had AEs considered severe.[12] The most frequently reported TEAEs were nausea, and URTIs. Other TEAEs that occurred in at least 3% were headache, nasopharyngitis, dizziness, acne, vomiting, abdominal pain, increased CPK, sinusitis, folliculitis, influenza, atopic dermatitis, cough, fever, and runny nose.[12] Discontinuation occurred in 2.1% (n = 2), 1.1% (n = 1), and 2.1% (n = 2) of participants in the abrocitinib 200 mg, 100 mg, and placebo groups, respectively.[12] One of the nausea TEAEs occurred in the abrocitinib 200 mg group and was considered severe enough to result in discontinuation of the study.[12] Other reasons for discontinuation of treatment were headache, gastroesophageal reflux, gastrointestinal infection, wound abscess, and URTI.[12]

Bieber and colleagues reported an AE incidence of 61.9%, 50.8%, 50%, and 53.4% for participants in the abrocitinib 200 mg, abrocitinib 100 mg, dupilumab, and placebo groups, respectively.[16] Severe AEs occurred in 1.8%, 2.1%, 0.8%, and 2.3% of the participants in the abrocitinib 200 mg, abrocitinib 100 mg, dupilumab, and placebo groups, respectively.[16] The AEs that were reported in at least 5% of participants in any group were nausea, conjunctivitis, nasopharyngitis, URTI, headache, and acne.[16] Discontinuations from AEs occurred in 4.4%, 2.5%, 3.3%, and 3.8% of the participants in the abrocitinib 200 mg, abrocitinib 100 mg, dupilumab, and placebo groups, respectively.[16]

Azathioprine

Study Characteristics

We identified 3 studies in 4 publications evaluating azathioprine for atopic dermatitis.[17,44,48,64] The 3 primary RCTs evaluated adults with moderate-to-severe disease with an active treatment period of 12 weeks.[17,44,48] A long-term extension study by Gerbens and colleagues provided an additional 5-year follow-up for participants, comparing azathioprine to methotrexate.[64] Efficacy outcomes included disease activity scales such as the Six-Area Six-Sign Atopic Dermatitis (SASSAD) severity score for older studies and SCORAD for more recent studies, as well as the IGA and the TBSA affected. Harm outcomes included AEs and hematologic abnormalities. All 3 RCTs were rated as having a *moderate* RoB, with all studies having relatively small sample sizes, ranging from 37 to 61 participants. Table 5 provides an overview of relevant study characteristics, with additional study information provided in Appendix B.

Table 5. Study Characteristics: Azathioprine for Atopic Dermatitis

Author, Year Trial Number Trial Name Risk of Bias	Participants	Product, Dose, Frequency	Study Design	Duration
Berth-Jones et al., 2002[48] Moderate	N = 37	Azathioprine 2.5 mg/kg/day Placebo	Randomized, double-blind, placebo controlled, crossover study	24 weeks (12 weeks each on azathioprine and placebo)
Meggitt et al., 2006[44] ISRCTN58943280 Moderate	N = 61	Azathioprine 1.0 to 2.5 mg/kg/day based on TPMT activity, n = 41 Placebo, n = 20	Randomized, double-blind, placebo controlled, parallel study	12 weeks active treatment with 6 months follow-up
Schram et al., 2011[17] Gerbens et al., 2018[64] Dutch Trial Registry NTR1916 Moderate	N = 42	Azathioprine 1.5 to 2.5 mg/kg/day, n = 22 Methotrexate 10 to 25 mg/week, n = 20	Randomized, single-blind, active controlled, parallel study	24 weeks
			Open label follow-up	5 years

Abbreviations. TPMT: thiopurine methyltransferase.

Berth-Jones and colleagues performed a randomized, double-blind, crossover study in 37 participants with severe disease.[48] Each participant received active treatment with azathioprine dosed at 2.5 mg/kg/day once daily for 12 weeks and a placebo control for 12 weeks for a total study period of 24 weeks on treatment.[48] The primary outcome was difference in the SASSAD score at the end of the treatment period.[48] Additional efficacy outcomes included improvement in sleep disturbance and level of work disruption based on a 10-cm visual analog scale (VAS).[48] This study did have notable attrition during the azathioprine study periods with 4 withdrawals due to noncompliance and 3 withdrawals due to AEs.[48]

Meggitt and colleagues reported results from a randomized, double-blind, parallel-group study in adults with moderate-to-severe disease.[44] Azathioprine dosing was based on thiopurine methyltransferase (TPMT) activity to minimize AEs, although average daily dose administered was not reported.[44] The study evaluated participants after 12 weeks of treatment with an additional 6 months of posttreatment follow up.[44] The primary outcome was SASSAD; additional outcomes included TBSA affected and the DLQI.[44]

Schram and colleagues performed a single-blind RCT comparing azathioprine to methotrexate in adult participants with severe atopic dermatitis who previously failed cyclosporine therapy.[17] Participants were initially treated and followed for 12 weeks, with an additional 12-week open-label follow up.[17] Azathioprine was titrated to a maximum dose of 2.5 mg/kg/day in a group of 22 participants, while methotrexate was administered up to 22.5 mg/week in 20 participants.[17] The primary efficacy outcome was the SCORAD scale at week 12; secondary outcomes included IGA assessment, EASI, and QoL as measured by the Skindex-17.[17] Harm outcomes included participant-reported AEs such as gastrointestinal upset, as well as laboratory assessments for

liver hepatic and hematologic function.[17] An additional 5-year follow-up was performed in 35 of these participants with 17 of those originally assigned to methotrexate and 18 assigned to azathioprine.[64] By the end of the 5-year study period only 7 were still receiving methotrexate and 4 were receiving azathioprine, with the remainder switching to topical therapy (n = 15), lost to follow-up (n = 5), or discontinued therapy (n = 5).[64]

Efficacy Outcomes

We rated the CoE for azathioprine clinical-related outcomes as *low*, while harm outcomes were rated as *moderate* (Table 2). Sample sizes for the studies were relatively small with short treatment durations overall; this is notable as atopic dermatitis is a chronic disease that waxes and wanes over time.

Berth-Jones and colleagues reported outcomes for 33 assessable participants treated with azathioprine and 28 assessable participants treated with placebo, out of 37 total participants enrolled in the crossover study design.[48] During azathioprine treatment participants improved on the SASSAD assessment by a mean of 10.2 points, going from a score of 39.7 at baseline to 29.6 at 12 weeks.[48] While receiving the placebo, participants improved by a mean of 1 point with a score of 33.6 and baseline and 32.6 at 12 weeks. This difference in score was significant in favor of azathioprine ($P < .01$).[48] Significant improvements were noted from baseline on the VAS for sleep disturbances and work disruption ($P < .01$ for each), although raw results were not reported.[48]

Meggitt and colleagues demonstrated improvement in SASSAD at 12 weeks, with participants in the azathioprine treatment group reporting a reduction of 12.0 points compared to 6.6 points for placebo (difference, 5.4 points; 95% CI, 1.4 to 9.3).[44] Both groups reported a SASSAD at baseline of approximately 32.5.[44] Participants reported a reduction in the TBSA involved of 25.8% with azathioprine and 14.6% with placebo (difference, 11.2%; 95% CI, 1.6% to 20.7%).[44] QoL as measured by the DLQI improved by 5.9 points with azathioprine treatment compared with 2.4 points with placebo (difference, 3.5 points; 95% CI, 0.3 to 32.3).[44] Extremely wide CIs for these reported outcomes are noted on the RoB assessments.

Schram and colleagues reported similar efficacy outcomes with azathioprine and methotrexate, with each group achieving a reduction of approximately 22.5 points ($P = .89$) on the SCORAD score from a baseline activity index of approximately 58 points.[17] Similar improvements were also seen in the improvement in IGA, EASI, and Skindex-17 measurements with no significant differences in any other efficacy measure.[17] For the long-term extension in these participants by Gerbens and colleagues, participants reported a total reduction in SCORAD at 5 years of 32.1 points for methotrexate and 32.1 points for azathioprine.[64] Other outcomes such as those with minimal disease, reduction in EASI, and improvement in Skindex-17 were similar between groups.[64]

Harm Outcomes

Berth-Jones and colleagues reported a high incidence of gastrointestinal AEs associated with azathioprine treatment, with 14 participants experiencing nausea, vomiting, diarrhea, bloating, and abdominal pain.[48] The AEs resulted in the withdrawal of 4 participants from the study.[48] One participant experienced mild neutropenia and lymphopenia at week 8 of azathioprine therapy;

another participant experienced lymphopenia at week 4 of azathioprine treatment.[48] Neither participant withdrew due to this AE.[48]

Notable AEs reported by Meggitt and colleagues included 18 of 41 (43%) participants receiving azathioprine experiencing at least 1 AE of mild lymphopenia.[44] This is notably higher than the incidence reported in similar studies for atopic dermatitis. Other common but less serious AEs include headache (5 of 41 [12%] for azathioprine, 3 of 20 [15%] for placebo) and abdominal pain (4 of 41 [10%] for azathioprine, 2 of 20 [10%] for placebo).[44] There were no reports of moderate or severe AEs in the placebo group; 7 of 41 (17%) reported moderate AEs and 4 of 41(10%) reported severe AEs (such as liver enzyme elevations) in the azathioprine group.[44]

Schram and colleagues reported that all 42 study participants (100%) recorded some type of AE.[17] Gastrointestinal AEs were common in both the azathioprine group and methotrexate group (55% and 59%, respectively; $P = .79$).[17] Infections were also common in both groups with 14 of 20 (70%) methotrexate recipients and 14 of 22 (64%) azathioprine recipients reporting study drug–related infections ($P = .19$).[17] One AE significantly higher in the azathioprine group was abnormalities in blood counts (mostly lymphopenia) with 17 of 22 (77%) experiencing this AE compared to 6 of 20 (30%) in the methotrexate group ($P < .01$).[17] In the 5-year follow-up to this study, 7 SAEs were reported with methotrexate including respiratory issues (n = 2), myocardial infarction (n = 2), and exacerbation of dermatitis (n = 1); 1 SAE was reported with azathioprine (exacerbation of dermatitis).[64]

Crisaborole

There were no new eligible studies found for this review. In a previous DERP systematic review and meta-analysis of 3 RCTs, participants treated with crisaborole were more likely to achieve response (44%) than participants on placebo vehicle (21%) based on the Atopic Dermatitis Severity Index.[65] The relative risk for this outcome was 1.67 (95% CI, 1.15 to 2.47); however, this analysis was performed in participants with mild-to-moderate atopic dermatitis, whereas this review is focused on moderate-to-severe disease.

Cyclosporine

Study Characteristics

We identified 9 RCTs in 10 publications analyzing cyclosporine for the treatment of atopic dermatitis: 2 RCTs evaluated against methotrexate, 1 RCT against enteric-coated mycophenolate sodium (EC-MPS), 1 RCT against prednisolone, 1 RCT against tacrolimus, 1 RCT against betamethasone dipropionate (BDP) cream, and 3 RCTs against placebo.[22-26,49-52,66] Seven were parallel group studies and 2 were crossover studies. All the studies were performed in international settings (e.g., Egypt, France, Finland, Germany, Italy, the Netherlands, and the UK). Two of these studies were noninferiority trials.[23,24] Eight of the 9 studies included adult populations, while El-Khalawany and colleagues included pediatric participants. Mean disease duration ranged from 6 to 26 years. Most studies had more male participants than female and had similar exclusion criteria (e.g., pregnancy or breastfeeding, hypertension, abnormal hepatic or renal function, HIV, systemic treatment, ultraviolet treatment, drugs known to interact with cyclosporine). Seven RCTs were rated as having a *high* RoB, and 2 rated as *moderate* RoB. Small sample sizes, ranging from 24 to 97 participants, was a major limitation in majority of the studies. The other primary limitations were blinding and high attrition. The most common efficacy

outcomes were SCORAD, EASI, DLQI, Rule of Nines Area Assessment (RoNAA), and VAS for itch and sleeplessness. All studies reported the harm outcomes as AEs except Granlund and colleagues. Five studies after the year 2000 used SCORAD as their primary outcome and had more meaningful answers to the key questions of this systematic review while the other 5 studies prior to 2000 focused on dated outcomes and were less contributive. Table 6 provides an overview of study characteristics of the included studies, with additional information provided in Appendix B.

Table 6. Study Characteristics: Cyclosporine for Atopic Dermatitis

Author, Year Trial Number Trial Name Risk of Bias	Participants	Product, Dose, Frequency	Study Design	Duration
Sowden et al., 1991[51] Salek et al. 1993[50] High	N = 33	Cyclosporine oral 5 mg/kg body weight/day for 8 weeks then placebo for 8 weeks, n = 17 Placebo then cyclosporine oral 5 mg/kg body weight/day for 8 weeks, n = 16	Randomized, double-blind, placebo-controlled, multicenter, crossover study	16 weeks
Munro et al., 1993[49] High	N = 24	Phase 1 (crossover): Cyclosporine oral 5 mg/kg body weight/day for 8 weeks, n = 12 Placebo, n = 12 Crossover for another 8 weeks: First cyclosporine then placebo: 9 First placebo then cyclosporine: 10 Phase 2 (17 participants agreed to continue dose-reduction plan): • Staged reductions in daily doses, reducing the daily dose of cyclosporine by 1 mg/kg every 2 weeks: 9 • Decreasing frequency of dosage, increasing the interval between doses by 1 day every 2 weeks: 8	Randomized, double-blind, placebo-controlled, crossover study	16 weeks
Van Joost et al., 1994[52] High	N = 46	Cyclosporine oral 5 mg/kg body weight/day for 6 weeks, n = 23 Placebo, n = 23	Randomized, double-blind, placebo-controlled, multicenter, parallel group study	6 weeks
Granlund et al., 1997[66] High	N = 41	Cyclosporine oral 3 mg/kg body weight/day, n = 16 BDP cream topically, n = 18 Run-in period: 4 weeks Treatment period: 6 weeks	Randomized, double-blind, controlled, single-center, parallel group study	12 weeks

Author, Year Trial Number Trial Name Risk of Bias	Participants	Product, Dose, Frequency	Study Design	Duration
Pacor et al., 2004[26] Moderate	N = 30	Cyclosporine 3 mg/kg body weight/day and placebo of tacrolimus (ointment without the drug for 6 weeks), n = 15 Tacrolimus 0.1% ointment twice daily, n = 15 Participants could use 1 or 2 tablets of cetirizine 10 mg as a rescue medication	Randomized, double-blind, double-dummy, placebo-controlled, parallel group study	6 weeks
Schmitt et al., 2010[25] High	N = 38	Cyclosporine 2.7 to 4.0 mg/kg body weight/day for 6 weeks, n = 17 Prednisolone 0.5 to 0.8 mg/kg for 2 weeks, then received placebo from week 3 to week 6, n = 21 All participants instructed to apply emollients twice daily	Randomized, observer-blinded, controlled, parallel study	18 weeks
Haeck et al., 2011[24] High	N = 50	Run in period: cyclosporine 5 mg/kg for 6 weeks, n = 55 Maintenance: Cyclosporine 3 mg/kg body weight/day divided in 2 oral doses for 30 days, n = 26 EC-MPS 1,440 mg for 30 days, n = 24	Randomized, observer-blinded, controlled parallel noninferiority study	48 weeks
El-Khalawany et al., 2013[22] Moderate	N = 40	Cyclosporine 2.5 mg/kg body weight/day divided in 2 oral doses, n = 20 Methotrexate 5 mg test dose, then 7.5 mg/week in a single oral dose for maintenance and supplemented with folic acid 400 µg once weekly, n = 20	Multicenter, randomized, parallel study	24 weeks
Goujon et al., 2018[23] High	N = 97	Cyclosporine 2.5 mg/kg body weight/day divided in 2 oral doses, n = 47 Methotrexate (15 mg/week in a single oral dose), n = 50	Phase 3, multicenter, randomized, evaluator-blinded, parallel group, noninferiority study	24 weeks

Abbreviations. BDP: beclomethasone dipropionate; EC-MPS: enteric coated mycophenolate sodium.

Goujon and colleagues conducted the largest study to date for cyclosporine (N = 97) in France, but it was still relatively small and we rated the study as *high* RoB.[23] The objective of this multicenter phase 3 noninferiority study was to examine whether methotrexate is as efficacious

as cyclosporine.[23] A total of 97 participants were included in this study: 50 participants in the methotrexate group and 47 in the cyclosporine group.[23] Baseline characteristics were similar in these 2 groups, but the cyclosporine group had a significantly higher average body weight than the methotrexate group.[23] In addition, the cyclosporine group had fewer female participants than the methotrexate group.[23] All participants in this study had long-term severe atopic dermatitis (median duration of ≥ 23 years in both groups, and eligible for systemic treatment).[23] Only 43% of participants in the methotrexate group received treatment for 24 weeks and completed the study compared to 77% participants in the cyclosporine group.[23] The primary outcome was the percentage of participants achieving SCORAD-50 (≥ 50% improvement from baseline in total SCORAD) at 8 weeks of treatment, and the lower limit of the one-sided CI (−20%) was decided as a noninferiority limit for the difference in SCORAD-50 proportions between 2 groups.[23] The total study duration was 24 weeks and this study was rated as having a *high* risk of bias.[23]

Similar to the study above, El-Khalawany and colleagues performed a *moderate*-RoB 24-week study comparing cyclosporine to methotrexate, but in a younger population (aged 8 to 14 years) with severe atopic dermatitis in Egypt.[22] This is the only study evaluating the effectiveness of cyclosporine in a pediatric population.[22] This study also had a higher percentage of male participants in the cyclosporine group versus the comparator group.[22] This study included only 40 participants, 20 in each treatment group.[22] To avoid SAEs, participants in the methotrexate group received low doses compared to the Goujon and colleagues study.[22] The primary outcome was absolute reduction in SCORAD score after 24 weeks; however, the outcomes were regularly assessed in every 4 weeks.[22]

Haeck and colleagues performed a *high*-RoB observer-blinded noninferiority RCT in the Netherlands comparing cyclosporine with EC-MPS and consisting of 3 distinct phases: 1) a 6-week run-in phase with higher doses of cyclosporine for all participants; 2) a 30-week treatment phase; and 3) a 12-week follow-up period.[24] Ten points was selected as the margin of noninferiority for the upper confidence limit.[24] This study also had more males in the cyclosporine group compared to the EC-MPS group.[24] The primary outcome was clinical disease activity measured using the objective SCORAD.[24] Both objective SCORAD scores and serum thymus and activation-regulated chemokine (TARC) levels were lower in the cyclosporine group compared to the EC-MPS group at baseline; however, it was unclear whether the difference was statistically significant.[24] Discontinuation occurred in all 3 phases of the study and the study outcomes were assessed in different weeks and in different phases until week 42.[24]

Schmitt and colleagues evaluated cyclosporine with prednisolone followed by placebo in another observer-blinded study in Germany, which we rated as *high* RoB.[25] A major bias (identified by the study authors) was using placebo in the prednisolone group for the last 4 weeks.[25] In addition, several participants also used cyclosporine previously, which brings selection bias and went unnoticed by the authors.[25] This study only had 38 adult participants: 17 in the cyclosporine group and 21 in the prednisolone group.[25] According to IGA scores (details in Appendix B), participants in the prednisolone group had more severe eczema compared to the cyclosporine group.[25] The participants needed to have a score of at least 40 on SCORAD and at least 10 on DLQI to be included.[25] All study participants had previously used topical glucocorticosteroids for treating atopic eczema.[25] The primary outcome was the proportion of participants with stable remission (relative improvement on the SCORAD-50) while in active treatment and no flare

(≥ 75% of baseline objective SCORAD after prior response) within the 12-week follow-up period.[25]

Pacor and colleagues focused on participants aged 13 to 45 years with long-term severe atopic dermatitis in a 6-week study assessing the clinical efficacy of oral cyclosporine compared with tacrolimus ointment in Italy.[26] We rated the study as *moderate* RoB. To be enrolled, participants needed to be treated with TCS and showed partial improvement to the treatment.[26] The study participants were allowed to use cetirizine 10 mg as a rescue medication.[26] This study included only 30 participants, with 15 in each group.[26] No statistically significant differences were observed in the baseline characteristics.[26] The primary outcome was SCORAD scores, with outcomes assessed every 7 days.[26] All study participants had sensitization to indoor allergens, asthma, rhinitis, and conjunctivitis.[26] No discontinuation occurred in the entire study including the follow-up period.[26]

Granlund and colleagues recruited participants with hand eczema from an outpatient clinic between 1992 and 1993 and performed a double-blind study with 2 phases including a 4-week run-in period and a 6-week treatment period, comparing oral cyclosporine with BDP ointment in Finland.[66] Participants who had treatment failure were transferred to the other treatment group for another 6 weeks.[66] We rated the study as *high* RoB. All the study participants had had eczema for at least 6 months with an inadequate response to conventional treatment.[66] Although 41 participants were randomized, only 34 completed the study.[66] For blinding purposes, participants in the oral cyclosporine group also used topical placebo cream, while participants in the topical BDP group received placebo capsules.[66] Significantly fewer participants used antibiotics prior to the study in the cyclosporine group compared to the BDP group.[66] The primary outcome was QoL assessed by Eczema Disability Index (EDI), which includes 5 dimensions (daily activity, work and school, personal relationship, leisure, and treatment).[66] Outcomes were assessed every 2 weeks.[66]

Van Joost and colleagues performed a 6-week *high*-RoB study comparing cyclosporine to placebo in 5 outpatient centers in the Netherlands.[52] This study included 46 participants (23 in each group), but only 14 participants in cyclosporine and 9 in placebo completed the study.[52] The cyclosporine group had more females than the placebo group.[52] The primary outcome included different clinical assessments such as severity of disease measured by TBSA, extent of disease measured by RoNAA, itch, sleep loss, and global efficacy, assessed every week.[52]

Munro and colleagues performed another industry-sponsored study in the United Kingdom (UK) that we rated as having a *high* RoB.[49] This crossover study only included 24 participants with 12 participants in each group.[49] In phase 1, the participants were treated for 8 weeks and then switched to another group for 8 more weeks.[49] A total of 17 participants agreed to continue another 4-week study plan that included either a gradual dose-reduction plan (reducing the daily dose of cyclosporine by 1 mg/kg every 2 weeks) or stepwise dose-reduction plan (maintaining dose at 5 mg/kg, but increasing the interval between doses by 1 day every 2 weeks).[49] Mean disease duration varied from 2 to 44 years.[49] The primary outcome was not specified in this study and all outcomes were assessed every 2 weeks until week 16.[49]

Sowden and colleagues reported findings from another UK-based 16-week crossover study with a *high* RoB, evaluating cyclosporine versus placebo in 33 adults.[51] This study included

participants from a wide age group (range, 16 to 58 years) and more males than females in both groups.[51] The primary outcomes were total disease activity including 6 clinical features and extent of disease measured by RoNAA.[51] Reported clinical assessments included disease activity, extent of disease, sleep and itch, topical steroid use, and tolerability.[51] Salek and colleagues published an additional analysis based on this same RCT focusing on the QoL assessments including both UK Sickness Impact Profile (UKSIP) and EDI.[50]

Efficacy Outcomes

We rated the overall CoE for cyclosporine compared with various treatments and placebo groups, for treatment of severe atopic dermatitis, as *very low*. Although 3 studies (in 4 publications) compared cyclosporine and placebo, the total sample size was 107 participants and none of these articles reported preferred efficacy outcomes such as SCORAD, EASI, IGA, and DLQI.[49-52] Two studies compared cyclosporine and methotrexate and the total sample size was 137; however, the target population was different for these 2 studies: 1 focused on adults while the other included pediatric participants.[22,23] All other comparisons had only 1 available study and small sample size ultimately contributed to the *very low* CoE.[24-26,66] Another major reason for *very low* CoE was RoB. Seven out of 9 studies were rated as having a *high* RoB.[23,25,49-52,66] For efficacy outcomes, cyclosporine could be similar to higher doses of methotrexate, EC-MPS, and prednisolone. Tacrolimus could be a better choice when compared to cyclosporine. Table 2 presents the GRADE ratings for cyclosporine and the narratives address this topic collectively.

In their study comparing cyclosporine to methotrexate, Goujon and colleagues reported significant differences in percentages of participants achieving SCORAD-50 response at week 8.[23] Methotrexate was found inferior to the cyclosporine because the 90% CI included zero.[23] After the dose increase, participants in the cyclosporine group had a statistically significant higher percentage achieving the primary outcome compared to the methotrexate group at both 12 and 24 weeks.[23] Although the findings for primary outcome was inconsistent between weeks, noninferiority was observed for EASI scores (a secondary study outcome) at weeks 20 and 24.[23] Overall, a notable increase was observed in the percentage of patients achieving SCORAD-50, 50% reduction in EASI (EASI-50), and DLQI at or below 5 outcomes in the methotrexate group after week 12.[23] Similar changes were not detected in the cyclosporine group.[23] The methotrexate dose was increased from 15 mg/week to 25 mg/week and the cyclosporine dose was increased from 2.5 mg/kg of body weight/day to 5 mg/kg of body weight/day after 12 weeks.[23] Outcomes were assessed every 4 weeks and results from each time point are presented in Appendix B.

In the pediatric study evaluating cyclosporine versus methotrexate, El-Khalawany and colleagues found that cyclosporine had a rapid onset of action and a rapid relapse compared to methotrexate.[22] Significant improvement in the SCORAD score was observed within each of the 2 groups immediately after treatment; however, no statistically significant differences between the treatment groups in SCORAD score were found at both the end of treatment period ($P = .93$) and the end of the 12 week follow-up period ($P = .29$).[22]

The 48-week noninferiority head-to-head study published by Haeck and colleagues reported a significant improvement in objective SCORAD ($P < .01$) and serum TARC levels ($P < .01$) while also had a positive effect on both QoL and VAS score for itch and sleeplessness in the first 6

weeks of treatment with cyclosporine compared with EC-MPS.[24] There was a worsening in the objective SCORAD score for the EC-MPS group resulting in a significant difference between the treatment groups at both week 3 and week 6.[24] Based on the margin of noninferiority, it was noted that EC-MPS was inferior to cyclosporine; however, a significant difference was not observed after 10 weeks.[24] The mean difference in objective SCORAD after 10 weeks of treatment was 0.8 points (95% CI, −4.4 to 6.0) until the end of the maintenance phase.[24] The objective SCORAD scoring trend over time was similar in the 2 treatment groups (P = .10).[24] Similar to the SCORAD score, serum TARC levels were also significantly different between treatment groups, favoring cyclosporine at both week 3 and week 6, but not after 10 weeks.[24] There was a difference in the frequency of prednisone (0.5 mg/kg) received in the treatment groups during the maintenance period: 7 participants in the EC-MPS for 7 days and none in the cyclosporine group.[24] There was also a significant difference in use of class III TCS between 2 groups during the early maintenance period (P = .01); the EC-MPS group used more class III TCS compared to the cyclosporine group after 3 weeks, but a significant difference was not observed after 18 weeks.[24] Although the authors claimed that the trend over time for the objective SCORAD was different between treatment groups, the significance value is misleading in this case (P = .049).[24] More participants in the cyclosporine group had a high QoL compared to the EC-MPS group in the first 6 weeks, but no differences were observed beyond that time.[24] During the follow-up period, there was an increase in the number of participants with low QoL in the cyclosporine group only.[24]

Schmitt and colleagues reported findings from a study comparing cyclosporine and prednisolone which terminated early after the preplanned interim analysis because of significant exacerbation of eczema.[25] The primary outcome, stable remission, was achieved in a higher percentage of participants receiving cyclosporine than those receiving prednisolone (35% vs. 5%; P = .03).[25] The response rate was not significantly different between the 2 treatment groups (P = .18).[25] In addition, at both end of active treatment and end of follow-up, no significant differences were observed between the 2 treatment groups for IGA, patient satisfaction, and DLQI.[25] Since 39% of the randomized participants withdrew from the study within the follow-up period, findings from this study should be interpreted carefully.[25]

Pacor and colleagues compared topical tacrolimus with oral cyclosporine in a double-blind randomized study and both treatment groups were treated with placebo.[26] The mean differences in SCORAD score between the 2 treatment groups was statistically significant, favoring tacrolimus in all weeks except for week 6, suggesting that tacrolimus may be a better choice when compared to cyclosporine (P < .01).[26] Additional efficacy parameters such as itching, erythema, and interference with sleep due to skin condition are reported in detail in the Appendix B.

Granlund and colleagues assessed the QoL using EDI in a study comparing oral cyclosporine with topical BDP.[66] Both treatment groups experienced statistically significantly similar improvement in the total EDI score; however, differences between the treatment groups at week 6 were not statistically significant.[66] Of the 5 dimensions in EDI, mean change from baseline for personal relationship and treatment were significantly different in the cyclosporine group (P < .05).[66] For the BDP group, daily activity and work/school dimensions were significantly different from baseline (P < .01).[66] Eight participants from cyclosporine and 12 participants from BDP

experienced treatment failure after the 6-week treatment period and were switched to the other treatment.[66] No significant differences were observed between the treatment groups at the end of the treatment.[66]

Van Joost and colleagues, Munro and colleagues, and Sowden and colleagues all evaluated the efficacy of cyclosporine in comparison to placebo.[49,51,52] Van Joost and colleagues reported that mean score of 6-area TBSA and RoNAA was improved abruptly in the cyclosporine group for the first 2 weeks, resulting a mean improvement of 55% for TBSA and 40% for RoNAA when compared to baseline at the end of treatment.[52] The placebo group experienced an increase in the disease activity score and no changes were observed for the RoNAA outcome.[52] All participants on cyclosporine had a significant response (i.e., percentage reduction of TBSA to baseline) of 75% or more.[52] Cyclosporine group had 35% improvement in the lichenification score compared to 14% improvement in the placebo group.[52] For both investigator and participant assessments, the differences between the treatment groups were statistically significant ($P < .01$).[52] At the end of the treatment, the cyclosporine group had a 1.6 point increase from baseline in mean scores of itch while the placebo group experienced only 0.5 points which was statistically significant ($P < .01$).[52]

Munro and colleagues evaluated 2 reducing-dose strategies for cyclosporine maintenance treatment.[49] Compared to placebo, all participants on cyclosporine experienced decreased severity and extent of eczema throughout the study period.[49] Area of active eczema, erythema, excoriation, and itch had the largest improvement among all the efficacy parameters.[49] Cyclosporine participants used 29 fewer units of topical steroid per week compared to the placebo users, and regardless of the ways to assess the topical steroid requirement, the difference between the 2 treatments was significant ($P < .01$).[49]

Sowden and colleagues reported findings from the earliest study on cyclosporine.[51] The cyclosporine group was favored over placebo with significantly lower scores in both disease activity and extent of disease outcomes.[51] Similarly, the VAS scores for itch and sleep were significantly different between the 2 treatment groups favoring cyclosporine ($P < .01$).[51] Salek and colleagues studied the same population as Sowden and colleagues and focused on the QoL outcomes including UKSIP and EDI.[50] For different items of UKSIP and EDI, both cyclosporine-placebo sequence and placebo-cyclosporine sequence showed significant changes from baseline to 8 weeks and 16 weeks ($P < .01$).[50] For the placebo-cyclosporine sequence, all the items of UKSIP and EDI had significant changes from baseline in either 8 weeks or 16 weeks or both ($P < .01$).[50] The cyclosporine-placebo sequence only observed the statistically significant changes in emotional behavior, alertness behavior, sleep and rest, daily activity, work/school, leisure, and treatment.[50] Excepting a few parameters, there was no relationship between QoL items and clinical assessments; however, there were several close correlations when the relationship between QoL parameters and VAS for sleep and itch were assessed.[50]

Harm Outcomes

Goujon and colleagues found the total number of AEs to not be significantly different between the cyclosporine and methotrexate treatment groups.[23] However, a significantly higher percentage of AEs ($P < .01$) related to the study drug was observed in the cyclosporine group compared to the methotrexate group.[23] Subjects with treatment-related AEs were higher in the

cyclosporine group than the methotrexate group.[23] The cyclosporine group reported only 1 SAE while the methotrexate group reported none.[23] More methotrexate users (12%) discontinued the study due to an AE compared to cyclosporine users (2%).[23] Participants in the cyclosporine treatment group experienced more nonskin infections, gastrointestinal disorders, neuromuscular disorders, dermatological disorders, and hypertension compared to the participants in the methotrexate group.[23]

El-Khalawany and colleagues reported more gastrointestinal manifestations and abnormal liver functions for the methotrexate group compared to the cyclosporine group.[22] In contrast, more general symptoms, hematopoietic AEs, and abnormal renal functions were recorded for the cyclosporine group compared to the methotrexate group.[22] Most importantly, all these AEs were absent after 24 weeks and there was no discontinuation because of the AEs.[22]

Haeck and colleagues reported AEs for all treatment scenarios: cyclosporine run-in phase, cyclosporine maintenance phase, and EC-MPS maintenance phase.[24] More AEs were observed in the cyclosporine run-in phase and cyclosporine maintenance phase compared to EC-MPS maintenance phase.[24] For example, 15% of the cyclosporine run-in phase participants had anemia while 4% participants using cyclosporine during the maintenance phase developed anemia.[24] In addition, 13% of cyclosporine users in run-in phase and 62% in maintenance phase experienced hypertrichosis.[24] None of the EC-MPS maintenance phase participants had anemia or hypertrichosis at all during the study.[24] Overall, participants in the cyclosporine run-in phase developed more severe AEs than the participants in the maintenance phase for those 2 treatment groups.[24]

Schmitt and colleagues reported 71 total AEs among the cyclosporine users compared to 57 total AEs in the prednisolone group.[25] Only 2 SAEs were reported for the prednisolone group while none reported for cyclosporine group.[25] Exacerbation occurred in more prednisolone participants compared to cyclosporine group.[25] Participants from the cyclosporine arm developed more common cold, arterial hypertension, headache, dysesthesia, and infection of the skin compared to the prednisolone users.[25] A higher number of discontinuations (52%) was observed in the prednisolone group compared to the cyclosporine group (29%), and almost all of them were because of exacerbation.[25] Two participants from the prednisolone group were admitted to hospital because of the exacerbation and withdrew from the study.[25]

Pacor and colleagues reported that cyclosporine and tacrolimus each had 4 AEs; all 8 AEs were mild in nature.[26] The authors did not find any changes in hematological and biochemical indices, blood pressure, heart rate, or atopic dermatitis exacerbation in the 2 treatment groups.[26] Only serum creatinine was moderately higher in the cyclosporine group.[26]

Granlund and colleagues did not assess safety.[66] Van Joost and colleagues, Munro and colleagues, and Sowden and colleagues all reported a higher number of AEs in the cyclosporine group compared to placebo.[49,51,52] Overall, 52% participants using cyclosporine developed an AE compared to 22% participants using placebo, in the study by Van Joost and colleagues; the number of participants experiencing severe AEs was equal in the 2 treatment groups.[52] Fifty-four percent and 18% of the total AEs had a probable and definite relationship to cyclosporine treatment, respectively.[52] Only 1 cyclosporine user discontinued the study because of an AE.[52] Most discontinuations occurred in the placebo group because of lack of response.[52] Munro and

colleagues reported a higher number of paraesthesia, rhinitis, gingivitis, hypertrichosis, menstrual disturbances, flushing, and gastrointestinal disturbance in the cyclosporine group compared to placebo.[49] A total of 4 participants did not complete the study phases because of irregular attendance and only 2 participants discontinued because of AEs.[49]

Sowden and colleagues found that 20 participants developed 39 AEs in the cyclosporine group while only 8 participants developed 8 AEs in the placebo group; the difference between the 2 groups was statistically significant ($P < .01$).[51] Two SAEs occurred in the placebo group while 1 SAE was observed in the cyclosporine group.[51] No discontinuation occurred because of AEs.[51] Participants failed to complete the study for reasons such as lack of placebo effect and treatment failure.[51] Salek and colleagues was a follow-up study of Sowden and colleagues targeting different outcomes, therefore reported similar AEs for both cyclosporine and placebo.[50]

Dupilumab

We did not identify any eligible studies comparing dupilumab to an already FDA-approved therapy. One study compared dupilumab with abrocitinib and another compared dupilumab with upadacitinib.[16,43] Each of these studies are discussed in their respective pipeline therapy sections.

In a previous DERP systematic review and meta-analysis, results from 6 placebo-controlled trials were pooled to assess likelihood of achieving and IGA response in participants with moderate to severe atopic dermatitis treated with dupilumab.[65] The pooled risk ratio for this outcome was 4.10 (95% CI, 3.10 to 5.42; $P < .01$) when comparing dupilumab with placebo.[65]

Omalizumab

Study Characteristics

We identified 1 eligible RCT comparing omalizumab to placebo in pediatric participants with atopic dermatitis.[31] This study evaluated children with severe disease over a 24-week treatment period, with an additional 24-week follow-up period; we rated it as having a *low* RoB. The primary efficacy outcome was the difference in SCORAD score at the end of the 24-week treatment period.[31] Secondary outcomes included the EASI score at endpoint.[31] A summary of relevant study characteristics is provided below in Table 7.

Table 7. Study Characteristics: Omalizumab for Atopic Dermatitis

Author, Year Trial Number Trial Name Risk of Bias	Participants	Product, Dose, Frequency	Study Design	Duration
Chan et al., 2020[31] NCT02300701 ADAPT Low	N = 62	Omalizumab dosed on plasma IgE concentrations and body weight, n = 30 Placebo, n = 32	Randomized, double-blind, parallel group, single center study	24 weeks

Abbreviation. IgE: immunoglobulin E.

Efficacy Outcomes

Chan and colleagues performed a study in 62 children at a single clinical site in the UK.[31] Participants were on average 10.3 years of age at enrollment with 30 randomized to receive omalizumab and 32 randomized to receive placebo.[31] Omalizumab was dosed based on body weight and total immunoglobulin E concentration at enrollment.[31] The primary efficacy outcome (change in SCORAD score at 24 weeks) was significantly improved in the omalizumab group with an adjusted mean difference of −8.3 points (95% CI, −15.1 to −1.1) although it fell short of achieving the minimal clinical important difference as defined by investigators (−8.7 points).[31] QoL assessments as measured by the CDLQI were significantly improved in the omalizumab group with a mean score difference of −3.5 (95% CI, −6.5 to −0.5); minimal clinical important difference was −3.3.[31]

Harm Outcomes

Chan and colleagues reported high incidences of AEs within the study, although worsening of atopic dermatitis was classified as a dermatologic AE, which made those reactions difficult to discern. Other AEs with a high reported incidence with both omalizumab and placebo were respiratory issues (15 of 30 [50%] and 25 of 32 [78%], respectively) and gastrointestinal issues (6 of 30 [20%] and 7 of 32 [22%], respectively).[31]

Pimecrolimus

Study Characteristics

We identified 1 eligible *moderate*-RoB RCT evaluating the efficacy and safety of pimecrolimus compared with TCS in infants with mild-to-moderate atopic dermatitis.[47] This was a 5-year open-label study with a primary outcome of IGA score of 0 or 1 (indicating clear or almost clear disease activity, respectively) and a secondary outcome of TBSA affected by inflammation.[47] A summary of relevant study characteristics is provided below in Table 8.

Table 8. Study Characteristics: Pimecrolimus for Atopic Dermatitis

Author, Year Trial Number Trial Name Risk of Bias	Participants	Product, Dose, Frequency	Study Design	Duration
Sigurgeirsson et al., 2015[47] NCT00120523 Moderate	N = 2,418	Pimecrolimus cream 1%, n = 1,205 Topical corticosteroid, n = 1,213	Randomized, open-label, parallel group study	5 years

Efficacy Outcomes

Sigurgeirsson and colleagues enrolled infants between 3 months and 12 months of age with mild-to-moderate disease into a 5-year study comparing pimecrolimus 1% cream with low- or medium-potency TCS.[47] Both groups reported rapid improvement in symptoms with 52.6% of those treated with pimecrolimus and 50.5% of those treated with TCS reporting treatment success (defined as IGA 0 or 1) by the third week.[47] At the end of the 5-year follow-up, 88.7% of those treated with pimecrolimus and 92.3% of those treated with TCS achieved treatment

success. By the end of the study participants assigned to pimecrolimus cream used the product a median of 224 days while participants assigned to TCS used the product a median of 178 days.[47] Thirty-six percent of participants in the pimecrolimus group did not use any rescue or other TCS at all.[47]

Harm Outcomes

Sigurgeirsson and colleagues reported high incidences of AEs with over 95% of both groups reporting an event.[47] The most common AEs reported for pimecrolimus and TCS respectively are nasopharyngitis (n = 711 [59%] vs. n = 715 [58.9%]), fever (n = 589 [48.9%] vs. n = 605 [49.9%]), bronchitis (n = 438 [36.3%] vs. n = 410 [33.8%]), and otitis media (n = 418 [34.7%] vs. 385 [31.7%]).[47] Other commonly reported AEs include diarrhea, upper respiratory infection, and cough.[47] SAEs were reported in 20.5% of pimecrolimus treated participants and 17.3% of topical steroid treated participants, although these events were not described further.[47]

Ruxolitinib

Study Characteristics

We identified 2 studies in 3 publications analyzing the use of ruxolitinib cream for moderate-to-severe atopic dermatitis: 1 phase-2 RCT, and 1 that reported results from 2 phase-3 RCTs.[38,39,53] Criteria for participation was similar across all studies; atopic dermatitis for at least 2 years, IGA score of 2 or 3, and TBSA involvement of 3% to 20%.[38,39] Additional study characteristics are provided in Table 9.

Table 9. Study Characteristics: Ruxolitinib for Atopic Dermatitis

Author, Year Trial Number Trial Name Risk of Bias	Participants	Product, Dose, Frequency	Study Design	Duration
Kim et al., 2020[39] Kim et al., 2021[53] INCB 18424-206 NCT03011892 Low	N = 307	Double-blind: Ruxolitinib 0.15% once daily, n = 51 Ruxolitinib 0.5% once daily, n = 51 Ruxolitinib 1.5% once daily, n = 52 Ruxolitinib 1.5% twice daily, n = 50 Triamcinolone 0.1% twice daily, n = 51 Vehicle twice daily, n = 52 Open-label to 1.5% ruxolitinib twice daily, n = 252	Randomized, double-blind, dose-ranging, vehicle and active-controlled, phase 2 trial	8 weeks
Papp et al., 2021[38] TRuE-AD1 TRuE-AD2 NCT03745638 Moderate	TRuE-AD1 N = 631 TRuE-AD2 N = 618	Ruxolitinib 0.75% twice daily, n = 252 (TRuE-AD1), n = 248 (TRuE-AD2) Ruxolitinib 1.5% twice daily, n = 253 (TRuE-AD1), n = 246 (TRuE-AD2) Vehicle twice daily, n = 126 (TRuE-AD1), n = 124 (TRuE-AD2)	Randomized, double-blind, vehicle-controlled, phase 3 clinical trial	8 weeks

Kim and colleagues conducted a *low*-RoB, phase 2, double-blind, dose-ranging, vehicle- and active-controlled trial to determine the efficacy of topical ruxolitinib cream in adults age 18 to 70 years.[39] Participants were randomized over 8 weeks to 1 of 6 groups; a vehicle control cream twice daily, triamcinolone 0.1% cream twice daily for 4 weeks followed by vehicle twice daily for 4 weeks (active control), or ruxolitinib cream at 0.15% once daily, 0.5% once daily, 1.5% once daily, or 1.5% twice daily.[39] After the 8 weeks, there was an open-label phase where participants could receive ruxolitinib 1.5% twice daily for 4 weeks.[39] The primary outcome was the mean change in EASI score at week 4 of ruxolitinib 1.5% twice daily versus placebo twice daily.[39] Secondary outcomes included change from baseline in EASI score for other concentrations of ruxolitinib, participants with IGA improvement, itch numeric rating scale, EASI-50, EASI-75, EASI-90 (90% reduction in EASI), and DLQI scores.[39] Safety and tolerability were assessed by monitoring for all treatment-emergent AEs (TEAEs) throughout the study duration and 4 weeks after the open-label period.[39] An additional analysis of QoL outcomes was also reported by Kim and colleagues.[53]

Papp and colleagues reported results from TRuE-AD1 and TruE-AD2, which were double blind, phase 3 clinical trials, rated as *moderate* RoB, in adolescents and adults with moderate-to-severe atopic dermatitis.[38] A washout period occurred which varied based on the atopic dermatitis treatment used previously. Participants received either ruxolitinib 0.75% cream, ruxolitinib 1.5% cream, or vehicle cream administered twice daily over 8 weeks.[38] Rescue treatments were not permitted. The TRuE-AD1 study included 631 participants and the TRuE-AD2 study included 618 participants.[38] The primary outcomes included the proportion of participants with IGA-treatment success (IGA-TS), defined as IGA 0 or 1 and ≥ 2-grade improvement from baseline at week 8.[38] Secondary endpoints included EASI-75, EASI-90, itch numeric rating scale, Patient-Reported Outcome Measurement Information System (PROMIS)-sleep disturbance item.[38] Safety and tolerability were assessed by clinical and laboratory monitoring for TEAEs.[38]

Efficacy Outcomes

Kim and colleagues demonstrated efficacy of ruxolitinib at all concentrations compared with vehicle placebo.[39] For the primary outcome (percentage change in EASI score at week 4), 1.5% ruxolitinib showed 71.6% change versus placebo with 15.5% change ($P < .01$).[39] The proportion of participants achieving EASI-50 and EASI-75 at week 4 was 78% and 56% for the ruxolitinib 1.5% versus 23.1% and 17.3% for placebo, respectively.[39] Percentage reductions from baseline in EASI at week 8 were 78.5% ($P < .01$), 67% ($P < .01$), 58.5% ($P < .01$), and 26.9% for participants receiving ruxolitinib 1.5% twice daily, ruxolitinib 1.5% once daily, ruxolitinib 0.5% once daily, and placebo, respectively.[39] The IGA response at week 4 and week 8 for the ruxolitinib 1.5% twice daily was 38% ($P < .01$) and 48% ($P < .01$), compared to 7.7% and 9.6% for placebo.[39] The mean change in Itch Numerical Rating Scale score from baseline were decreased in all groups through week 4 with the largest decrease occurring in the ruxolitinib 1.5% twice daily and once daily groups.[39,53]

In both TRuE-AD1 and TRuE-AD2, ruxolitinib achieved IGA-TS versus placebo at week 8, with 50% ($P < .01$) and 39% ($P < .01$) for ruxolitinib 0.75%, and 53.8% ($P < .01$) and 51.3% ($P < .01$) for ruxolitinib 1.5%, respectively.[38] With odds ratios (ORs) of 6.4 (95% CI, 3.6 to 11.9) and 8.8 (95% CI, 4.1 to 21.1) for ruxolitinib 0.75%, 7.5 (95% CI, 4.2 to 14) and 15.8 (95% CI, 7.4 to 38.1) for ruxolitinib 1.5% in the TRuE-AD1 and TRuE-AD2, respectively.[38] In TRuE-AD1 participants who

achieved an EASI-75 response at week 8 were 56% ($P \leq .01$), 62.1% ($P \leq .01$), and 24.6% for ruxolitinib 0.75%, ruxolitinib 1.5%, and placebo, respectively.[38] In TRUE-AD2 participants who achieved an EASI-75 response at week 8 were 51.5% ($P \leq .01$), 61.8% ($P \leq .01$) and 14.4% for ruxolitinib 0.75%, ruxolitinib 1.5%, and placebo, respectively.[38] The mean percentage change from baseline in EASI score for TRuE-AD1 and TRuE-AD2 was −72.2 ($P \leq .01$) and −74.8 ($P \leq .01$) for ruxolitinib 0.75%, −77.2($P \leq .01$) and −74.7 ($P \leq .01$) for ruxolitinib 1.5%, and −40.5% and −28.9% for vehicle, respectively.[38] Clinically relevant reductions in Itch Numerical Rating Scale score were seen in ruxolitinib participants versus placebo for both TRuE-AD1 and TRuE-AD2; 40.4% and 42.7% for ruxolitinib 0.75%, 52.2% and 50.7% for ruxolitinib 1.5%, 15.4%, and 16.3% for placebo ($P < .01$), respectively.[38] In TRuE-AD1, ruxolitinib demonstrated improvement (≥ 6 point improvement from baseline) versus placebo in PROMIS-sleep disturbance item ($P < .01$).[38]

Harm Outcomes

During the 8-week double-blind period, Kim and colleagues reported TEAEs for 24% (12 of 50) of the ruxolitinib 1.5% twice daily group, 33.3% (17 of 51) of the ruxolitinib 1.5% once daily group, 21.6% (11 of 51) for the ruxolitinib 0.5% once daily group, 37.3% (19 of 51) for the ruxolitinib 0.15% daily group, 33.3% (17 of 51) for the triamcinolone group, and 32.7% (17 of 52) for the vehicle group.[39] One serious TEAE (myocardial infarction) was reported in the triamcinolone group and deemed unrelated to treatment. Three participants discontinued overall due to atopic dermatitis (vehicle), uvulitis (triamcinolone), and eczema (ruxolitinib 0.15%).[39] The most frequent TEAEs in the double-blind period and open-label period included headache, nasopharyngitis, URTI, urinary tract infection, application-site pain, and atopic dermatitis.[39] Application-site pain was the most frequent TEAE in all the ruxolitinib groups and vehicle group.[39]

For TRuE-AD1 and TRuE-AD2, TEAEs were pooled and reported as 29% (145 of 500) for 0.75% ruxolitinib, 26.5% (132 of 499) for ruxolitinib 1.5%, and 33.2% (83 of 250) for vehicle.[38] Serious TEAEs were reported in 0.6% (0.75% ruxolitinib) and 0.8% (1.5% ruxolitinib and vehicle groups) of participants.[38] The most frequently reported AEs (> 1% of total pooled population) were nasopharyngitis, headache, URTI, application site burning, application site itching, and atopic dermatitis.[38] Overall discontinuation occurred in 0.8% of the ruxolitinib 0.75%, 0.8% of the ruxolitinib 1.5%, and 3.2% of the placebo groups.[38]

Tacrolimus

There were no additional eligible studies found for this review regarding treatment with tacrolimus. One study compared tacrolimus with cyclosporine and is discussed in the cyclosporine section.[26] A previous DERP systematic review and meta-analysis indicated there were no significant difference between tacrolimus and pimecrolimus for efficacy, while tacrolimus was superior to TCS in participants with moderate-to-severe atopic dermatitis.[65]

Tralokinumab

Study Characteristics

We identified 4 RCTs in 3 publications analyzing tralokinumab for the treatment of moderate-to-severe atopic dermatitis: 1 phase-2b RCT, 3 phase-3 RCTs, and 1 post hoc analysis.[32-34] Efficacy outcomes evaluated disease burden and itching through tools validated to measure atopic dermatitis including EASI and IGA.[32-34] QoL was evaluated through the DLQI and other tools.[32-35]

Harm outcomes included TEAEs.[32-34] Studies were rated as *low* to *moderate* RoB.[32-34] Table 10 provides additional information on the 4 RCTs.

Table 10. Study Characteristics: Tralokinumab for Atopic Dermatitis

Author, Year Trial Number Trial Name Risk of Bias	Participants	Product, Dose, Frequency	Study Design	Duration
Wollenberg et al., 2019[34] Silverberg et al., 2021[35] NCT02347176 Moderate	N = 204	Tralokinumab 45 mg SQ every 2 weeks, n = 50 Tralokinumab 150 mg SQ every 2 weeks, n = 51 Tralokinumab 300 mg SQ every 2 weeks, n = 52	Randomized, double-blind, placebo-controlled, phase-2b multicenter, dose-ranging study	12 weeks 10-week follow-up
Wollenberg et al., 2021[33] ECZTRA 1 ECZTRA 2 NCT03160885 NCT03131648 Low	N = 1596 (ECZTRA 1 n = 802 ECZTRA 2 n = 794)	Tralokinumab 300 mg every 2 weeks (600 mg LD) ECZTRA 1, n = 603 ECZTRA 2, n = 593	Identical, randomized, double-blind, placebo-controlled, international studies	16 weeks 36-week maintenance
Silverberg et al., 2021[32] ECZTRA 3 NCT03363854 Low	N = 380	Tralokinumab 300 mg SQ every 2 weeks (600 mg LD), n = 253	Randomized, double-blind, placebo-controlled, international study	16 weeks 16-week extension

Abbreviations. SQ: subcutaneous; LD: loading dose.

Wollenberg and colleagues conducted a multicenter, phase 2b, placebo-controlled, dose-ranging study.[34] This 12-week study included adults with moderate to severe atopic dermatitis, an EASI of 12 or more, a SCORAD of 25 or more, an IGA of 3 or more, and involvement of 10% TBSA or more, and had a 10-week follow-up extension.[34] Investigators randomized participants to 45 mg, 150 mg, or 300 mg of tralokinumab, or placebo every 2 weeks.[34] Investigators gave participants class III TCS that were continued through the treatment phase of the study.[34] Investigators allowed use of rescue therapy as long as it was not systemic or topical calcineurin inhibitors.[34] Wollenberg and colleagues also evaluated a high dipeptidyl-peptidase 4 group and high periostin group, both of which are submarkers for IL-13.[34]

The primary outcomes included EASI change from baseline to week 12, and IGA of 0 to 1 with reduction of 2 grades or more.[34] Secondary outcomes included change from baseline in EASI and SCORAD scores, EASI-50, SCORAD-50, and achievement of an IGA of 0 to 1 at each visit up to week 22.[34] Secondary quality measures evaluated DLQI at week 22.[34] Silverberg and colleagues conducted a post hoc analysis of quality measures including the DLQI, short form 36-item health survey version 2 (SF-36v2) separated into a physical component summary (PCS) and mental

component summary (MCS), and sleep interference numerical rating scale from baseline to 12 weeks. Safety outcomes included TEAE.[35]

Wollenberg and colleagues conducted 2 identical multinational, phase-3 studies named ECZTRA 1 and ECZTRA 2.[33] Wollenberg and colleagues included adults with moderate-to-severe atopic dermatitis for 1 or more years, 1 year of inadequate response to TCS, an EASI of 12 or more and IGA of 3 or more, and involvement of at least 10% TBSA.[33] Investigators included participants with an IGA of 0 to 1 or improvement in EASI by 75% or more into a 36-week maintenance phase.[33] Investigators randomized participants to tralokinumab 300 mg (600 mg loading dose) every 2 weeks or placebo for 16 weeks.[33] Investigators randomized participants in the 36-week maintenance phase to tralokinumab 300 mg every 2 weeks, every 4 weeks, or placebo.[33] Investigators instructed all participants to use emollients twice daily.[33] Rescue therapy with TCS and systemic glucocorticoids was allowed.[33] Investigators labeled participants who received systemic rescue therapy as nonresponders.[33]

The primary outcomes included achievement of an IGA of 0 to 1, and improvement of EASI by 75% or more at 16 weeks and 52 weeks.[33] Secondary endpoints included a SCORAD change from baseline, DLQI Change from baseline, POEM change from baseline, EASI change from baseline, achievement of a 50% and 90% improvement in EASI, worst daily itching and TCS use, and reduction of DLQI by 4 or more at 16 weeks.[33] Safety outcomes included TEAEs.[33]

Silverberg and colleagues conducted a multinational, phase 3 study named ECZTRA 3.[32] Investigators stratified participants before randomization by region and IGA score of 3 or 4.[32] This study had the same inclusion criteria as ECZTRA 1 and ECZTRA 2.[32] Investigators randomized participants to tralokinumab 300 mg (600 mg loading dose) every 2 weeks or placebo, with TCS use allowed in both groups on an as-needed basis.[32] Investigators instructed those requiring TCS to apply a thin layer of medium-potency TCS as needed.[32] Investigators allowed rescue therapy with topical and systemic therapy.[32]

Efficacy Outcomes

CoE for tralokinumab was rated as *very low* to *moderate*. Table 2 describes the summary of GRADE findings.

Wollenberg and colleagues only showed significant improvement in EASI with tralokinumab 150 mg (mean difference, −4.36; 95% CI, −8.22 to −0.51; $P = .03$) and 300 mg (mean difference, −4.94; 95% CI, −8.76 to −1.13; $P = .01$) at 12 weeks.[34] The 300-mg dosage showed similar results in the high dipeptidyl-peptidase 4 group and high periostin group at 12 weeks.[34] Secondary results showed an improvement in EASI-50 with tralokinumab 300 mg over placebo (73.4% vs 51.9%, respectively; $P = .03$) and EASI-75 with tralokinumab 300 mg over placebo (42.5% vs 15.5%, respectively; $P < .01$) at 12 weeks.[34] Tralokinumab 150 mg and 300 mg dosages showed significant improvements in SCORAD compared to placebo (mean difference, −9.42; [95% CI, −15.56 to −3.29; $P < .01$] and −9.84 [95% CI, −15.91 to −3.77; $P < .01$] respectively) at 12 weeks.[34] Tralokinumab 150 mg and 300 mg dosages showed significant improvement in SCORAD-50 over placebo (44.2%; $P < .01$ and 44.1%; $P < .01$, respectively) at 12 weeks.[34] Tralokinumab showed benefit in SCORAD as early as week 2.[34] Tralokinumab 300 mg dosage

showed significant improvement in DLQI (−3.51; 95% CI, −6.00 to −1.02; *P* < .01); however this benefit was not maintained beyond 12 weeks.[34]

In the post hoc analysis, Silverberg and colleagues showed change at 6 and 12 weeks for DLQI was only significant in the 300 mg group over placebo at 12 weeks (−6.77 vs. −3.26; 95% CI, −6.00 to −1.02; *P* < .01).[35] Tralokinumab 300 mg showed significant reduction over placebo on the SF-36v2 MCS, and significant in all doses over placebo with SF-36v2 PCS and sleep.[35] Results for tralokinumab 300 mg versus placebo with SF-36v2 MCS was 5.41 versus 1.18 (95% CI, 0.98 to 7.47; *P* < .01), SF-36v2 PCS was 4.05 versus −0.21 (95% CI, 1.83 to 6.6; *P* < .01), and sleep numerical rating scale was −1.96 versus −0.71 (95% CI, −2.09 to −0.40; *P* < .01), respectively.[35]

Wollenberg and colleagues reported significant improvement over placebo in achieving an IGA of 0 to 1 (difference of 8.6%, [95% CI, 4.1 to 13.1; *P* < .01] and difference of 11.1% [95% CI, 5.8 to 16.4; *P* < .01] in ECZTRA 1 and ECZTRA 2 respectively) and an EASI reduction of 75% (difference of 12.1% [95% CI, 6.5 to 17.7; P < .001] and difference of 21.6% [95% CI, 15.8 to 27.3; *P* < .01] in ECZTRA 1 and ECZTRA 2 respectively).[33] Results from the maintenance phase only showed significance in achieving an IGA of 0 to 1 in ECZTRA 2 for tralokinumab every 2 weeks over placebo (difference of 34.1%; 95% CI, 13.4 to 54.9; *P* < .01).[33] Tralokinumab showed significance in achieving EASI-75 for every 2 weeks and every 4 weeks over placebo only in ECZTRA 2 (difference of 33.7 [95% CI, 17.3 to 50.0; *P* < .01] every 2 weeks and difference of 30.0% [95% CI, 13.7 to 46.4; *P* < .01] every 4 weeks).[33] Secondary results showed significant improvements over placebo with SCORAD (difference of 10.4 [95% CI, −14.4 to −6.5; *P* < .01] in ECZTRA 1 and difference of −14 [95% CI, −18 to −10.1; *P* < .01] in ECZTRA 2) and DLQI (difference of −2.1, [95% CI, −3.4 to −0.9; *P* < .01] in ECZTRA 1 and difference of −3.9 [95% CI, −5.2 to −2.6; *P* < .01] in ECZTRA 2).[33] Benefit was demonstrated in week 2 and onwards for SCORAD and DLQI.[33]

Silverberg and colleagues showed an improvement in achieving an IGA of 0 to 1 with tralokinumab over placebo (38.9% vs. 26.2%; 95% CI, 2.9 to 21.9; *P* = .02) and achieving a 75% EASI reduction with tralokinumab over placebo, (56% vs. 35.7%; 95% CI, 9.8 to 30.6; *P* < .01).[32] Silverberg and colleagues showed continued benefit in all outcomes at 32 weeks.[32] Secondary results showed improvement in SCORAD (difference, −10.9; 95% CI, −15.2 to −6.6; *P* < .01) and DLQI (difference, −2.9; 95% CI, −4.3 to −1.6) over placebo.[32] SCORAD and DLQI showed significant results starting at week 2.[32]

Harm Outcomes

Wollenberg and colleagues showed most AEs with tralokinumab were mild to moderate.[34] Common AEs occurring more than 5% include nasopharyngitis (11.8% to 23.1%), URTI (7.7% to 10%), headache (6% to 7.8%), and atopic dermatitis (5.8% to 6.0%).[34] The most common treatment-related AE was URTI at 3.9% overall, versus 3.9% with placebo.[34]

Wollenberg and colleagues showed most AE with tralokinumab were mild to moderate.[33] Common AEs occurring more than 5% include atopic dermatitis (16.6% to 25.9%), URTI (8.3% to 23.1%), conjunctivitis (3.1% to 7.1%), and itching (2.5% to 5.3%).[33]

Silverberg and colleagues showed most AEs with tralokinumab were mild to moderate.[32] Common AE occurring more than 5% included viral URTI (19.4%), conjunctivitis (11.1%), headache (8.7%), URTI (7.5%), and injection site reaction (6.7%).[32] Continuation phase showed similar AEs with the addition of oral herpes and nausea in 5.8% of participants on tralokinumab every 4 weeks.[32]

Upadacitinib

Study Characteristics

For upadacitinib, we identified 4 RCTs: 3 placebo-controlled trials and 1 head-to-head trial with dupilumab.[40-43] All studies confirmed moderate-to-severe atopic dermatitis diagnosis with IGA-AD of 3 or more, EASI score of 16 or more, and TBSA of at least 10% for at least 1 year before initiation of study.[40-42] Efficacy outcomes included percentage improvement in EASI, EASI-75, EASI-50, IGA-AD, Itch Numerical Rating Scale, SCORAD, POEM, and DLQI.[40-42] Harm outcomes included incidence and severity of AEs.[40-42] We rated studies as having a *low* or *moderate* RoB. Table 11 provides an overview of the pertinent study characteristics.[40-42]

Table 11. Study Characteristics: Upadacitinib for Atopic Dermatitis

Author, Year Trial Number Trial Name Risk of Bias	Participants	Product, Dose, Frequency	Study Design	Duration
Guttman-Yassky et al., 2020[40] NCT02925117 Low	N = 167	Upadacitinib 7.5 mg once daily, n = 42 Upadacitinib 15 mg once daily, n = 42 Upadacitinib 30 mg once daily, n = 42 Placebo daily, n = 41	Randomized, double-blind, placebo-controlled, parallel-group, phase 2b, dose-ranging clinical trial	16 weeks
Reich et al., 2021[41] AD Up NCT03568318 Low	N = 901	Upadacitinib 15 mg daily and TCS, n = 300 Upadacitinib 30 mg daily and TCS, n = 297 Placebo daily and TCS, n = 304	Randomized, double-blind, placebo-controlled, phase 3 clinical trial	16 weeks
Guttman-Yassky et al., 2021[42] Measure Up 1 Measure Up 2 NCT03569293 Low	N = 847	Upadacitinib 15 mg daily: n = 281 (Measure Up 1); n = 276 (Measure Up 2) Upadacitinib 30 mg daily: n = 285 (Measure Up 1); n = 282 (Measure Up 2) Placebo daily: n = 281 (Measure Up 1); n = 278 (Measure Up 2)	Randomized, double-blind, placebo-controlled, phase 3 clinical trials	16 weeks

Author, Year Trial Number Trial Name Risk of Bias	Participants	Product, Dose, Frequency	Study Design	Duration
Blauvelt et al., 2021[43] HEADS Up NCT03738397 Moderate	N = 692	Upadacitinib 30 mg daily, n = 348 Dupilumab 300 mg every 2 weeks, n = 344	Randomized, double-blind, double-dummy, active-controlled, phase 3b clinical trial	24 weeks

Abbreviation. TCS: topical corticosteroids.

Guttman-Yassky and colleagues conducted a double-blind, phase 2b, placebo-controlled, parallel-group, dose-ranging trial to determine efficacy of once daily upadacitinib monotherapy in adults (18 to 75 years) over 16 weeks.[40] For enrollment, the EASI score must be at least 12, TBSA involvement of at least 10%, and atopic dermatitis diagnosis for at least 2 years.[40] The primary outcome was the percentage improvement EASI at week 16.[40] Secondary outcomes included EASI-50, EASI-75, EASI-90, proportion of participants with IGA improvement, Itch Numerical Rating Scale, SCORAD-50, SCORAD-75 (75% improvement), SCORAD-90 (90% improvement), and change from baseline in TBSA, POEM, and DLQI scores.[40] Safety and tolerability were assessed by monitoring changes from baseline in physical exam, vital signs, and laboratory tests.[40]

The AD Up study by Reich and colleagues was a randomized, double-blind, phase 3 clinical trial comparing the efficacy and safety of upadacitinib 30 mg and 15 mg in combination with TCS therapy in adolescents (12 to 17 years) and adults (18 to 75 years) with moderate-to-severe atopic dermatitis.[41] All participants concomitantly received protocol-mandated (step-down) TCS along with daily emollients.[41] Rescue therapy was allowed from week 4 for worsening atopic dermatitis symptoms.[41] In some countries topical calcineurin inhibitors, crisaborole, or both could be used instead of TCS.[41] A total of 901 participants completed the study at 171 centers.[41] The primary outcomes included the proportion of participants who achieved EASI-75 and a vIGA-AD response at week 16.[41] Secondary outcomes included Worst Pruritis Numerical Rating Scale (WP-NRS) score improvement, EASI-90, EASI-75 at various time points, mean TCS free days, and median time to discontinuation of TCS.[41] All TEAEs were assessed by laboratory monitoring, vital signs and clinical assessments at scheduled study visits and within 30 days after last dose.[41]

Measure Up 1 and 2 are double-blind, placebo-controlled, phase 3 trials reported by Guttman-Yassky and colleagues.[42] Measure Up 1 (N = 847) was conducted at 151 centers; Measure Up 2 (N = 836) was conducted at 154 centers.[42] Participants were adolescents (12 to 17 years, ≥ 40 kg) or adults (18 to 75 years) randomized to upadacitinib 30 mg, upadacitinib 15 mg, or placebo, administered orally once daily for 16 weeks.[42] An emollient applied twice daily 7 days before baseline and during the study was required but no other therapies were allowed.[42] Rescue therapy was allowed after week 4.[42] The primary outcomes were the proportion of participants achieving EASI-75, and vIGA-AD response at week 16.[42] Secondary outcomes included proportion of participant with improvement in WP-NRS score, EASI-90, EASI-75, atopic dermatitis flares, Atopic Dermatitis Impact Scale (ADerm-IS) sleep domain, Atopic Dermatitis

Symptom Scale (ADerm-SS), POEM, DLQI, Hospital Anxiety and Depression Scale-Anxiety (HADS-A) and percent change in EASI at week 16 and other study points.[42] TEAEs were assessed and monitored with laboratory monitoring and vital signs recorded throughout the study and 30 days after the last dose.[42] Since this trial occurred during the COVID-19 pandemic, accommodations were made for site disruptions and remote visits.[42] Remote efficacy assessments of skin conditions were not allowed.[42]

Blauvelt and colleagues reported on HEADS Up, a double-blind, double-dummy, active-controlled, phase 3b, 24-week trial comparing the efficacy and safety of upadacitinib 30 mg daily versus dupilumab 300 mg every 2 weeks in adults (18 to 75) with moderate to severe atopic dermatitis.[43] Participants had to be candidates for systemic therapy defined as having an inadequate response to topical treatments, documented use of systemic treatment, or topical treatments otherwise medically inadvisable.[43] Rescue therapy could be given at any time per investigator discretion.[43] The primary outcomes was EASI-75 response at week 16.[43] Secondary outcomes included percent change in Worst Pruritus Numerical Rating Scale, EASI-100 (100% improvement in EASI), and EASI-90, at weeks 4, 16, and 24.[43] Safety and tolerability were assessed as TEAEs in all participants who received more than 1 dose of study drug through 30 days after last dose of upadacitinib or dupilumab.[43]

Efficacy Outcomes

Upadacitinib 30 mg and 15 mg achieved efficacy over placebo in all primary outcomes (improvement in EASI, EASI-75 and vIGA-AD) across studies.[40-43] The upadacitinib groups also demonstrated significant efficacy for most of the secondary endpoints.[40-43]

Guttman-Yassky and colleagues reported all upadacitinib doses showed significant improvement in EASI from baseline at week 16.[40] The mean improvement from baseline was 74% ($P \leq .01$), 62% ($P \leq .01$), 39% ($P \leq .05$), and 23% for upadacitinib 30 mg, 15 mg, 7.5 mg, and placebo, respectively.[40] The mean difference for percentage improvement from baseline in EASI versus placebo was 51% (95% CI, 36% to 67%), 39% (95% CI, 24% to 54%), 16% (95% CI, 1.4% to 31%), for upadacitinib 30 mg, 15 mg, and 7.5 mg, respectively.[40] EASI-50, EASI-75 and EASI-90 was achieved by all doses of upadacitinib and was statistically significantly greater versus placebo.[40] Itch Numerical Rating Scale, SCORAD outcomes, mean percentage reductions in TBSA and POEM scores all favored upadacitinib compared with placebo.[40]

The efficacy of upadacitinib with TCS was reported in the AD Up study by Reich and colleagues.[41] For the primary endpoint of EASI-75, the proportion of participants achieving this was 77.1% (95% CI, 72.3 to 81.9), 64.6% (95% CI, 59.1 to 70), and 26.4% (95% CI, 21.5 to 31.4) for the upadacitinib 30 mg plus TCS, upadacitinib 15 mg plus TCS, and placebo plus TCS, respectively.[41] The vIGA-AD at week 16 was achieved for 58.6% (95% CI, 53 to 64.2) of upadacitinib 30 mg plus TCS participants, 39.6% (95% CI, 34.1 to 45.2) of upadacitinib 15 mg plus TCS participants, and 10.9% (95% CI, 7.4 to 14.4) of placebo plus TCS participants.[41] The total EASI percent change at week 16 from baseline was −87.3 (95% CI, −83.4 to −91.2), −78 (95% CI, −74.1 to −81.9), and −45.9 (95% CI, −41.6 to −50.1) for upadacitinib 30 mg plus TCS, upadacitinib 15 mg plus TCS, and placebo plus TCS, respectively.[41] The proportion of participants achieving WP-NRS response for the upadacitinib 30 mg plus TCS group, upadacitinib 15 mg plus TCS group, and placebo plus TCS was 63.9% (186 of 291; 95% CI, 58.4

to 69.4), 51.7% (149 of 288; 95% CI, 46 to 57.5) and 15% (44 of 294; 95% CI, 10.9 to 19), respectively.[41]

Measure Up 1 and Measure Up 2 demonstrated upadacitinib efficacy for the primary endpoints.[42] For Measure Up 1, the proportion of participants who achieved EASI-75 was 79.7% (227 of 285; 95% CI, 75 to 84.4), 69.6% (196 of 281; 95% CI, 64.2 to 75) and 16.3% (46 of 281; 95% CI, 12 to 20.7) for upadacitinib 30 mg, upadacitinib 15 mg, and placebo, respectively.[42] The proportion of participants who achieved vIGA-AD response was 62% (177 of 285; 95% CI, 56.4 to 67.7), 48.1% (135 of 281; 95% CI, 42.3 to 54), and 8.4% (24 of 281; 95% CI, 5.2 to 11.7) for upadacitinib 30 mg, upadacitinib 15 mg and placebo, respectively.[42] In Measure Up 2, the participants who achieved EASI-75 was 72.9% (206 of 282; 95% CI, 67.7 to 78.2), 60.1% (166 of 276; 95% CI, 54.4 to 65.9), and 13.3% (37 of 278; 95% CI, 9.3 to 17.3) for upadacitinib 30 mg, upadacitinib 15 mg, and placebo, respectively.[42] The proportion of participants who achieved vIGA-AD response was 52% (147 of 282; 95% CI, 46.1 to 57.9), 38.8% (107 of 276; 95% CI, 33 to 44.5), and 4.7% (13 of 278; 95% CI, 2.2 to 7.2) for upadacitinib 30 mg, upadacitinib 15 mg and placebo, respectively.[42] The change in SCORAD from baseline at week 16 was −73.1 (95% CI, −76.5 to −69.7) and −68.4 (95% CI, −72.4 to −64.4) for upadacitinib 30 mg, −65.7 (95% CI, −69.2 to −62.2) and −57.9 (95% CI, −61.8 to −54) for upadacitinib 15 mg, and −32.7 (95% CI, −37.3 to −28) and −28.4 (95% CI, −33.3 to −23.5) for placebo in the Measure Up 1 and Measure Up 2 trials, respectively.[42] For other secondary endpoints such EASI-90, EASI-100, as ADerm-SS, POEM, DLQI improvement, change in WP-NRS, and atopic dermatitis flare upadacitinib 30 mg and upadacitinib 15 mg achieved statistical significance over placebo ($P < .0001$).[42] Upadacitinib 30 mg and 25 mg achieved an EASI-75 response at week 1 and was maintained throughout all other time points up to week 16.[42]

Heads Up showed that upadacitinib (71%, 247 of 348; 95% CI, 66.2 to 75.8) was superior to dupilumab (61.1%, 210 of 344; 95% CI, 55.9 to 66.2) for the primary end point of EASI-75 at week 16, with an adjusted difference of 10% (95% CI, 2.9% to 17%; $P = .006$).[43] The percent Worst Pruritus Numerical Rating Scale improvement at week 16 from baseline was greater for upadacitinib than dupilumab, −66.9% (95% CI, −70.6 to −63.2) versus −49% (95% CI, −52.9 to −45.2) ($P < .01$), respectively.[43] Clinically relevant improvement (≥ 4 points) in the Worst Pruritus Numerical Rating Scale score occurred in 55.3% (188 of 348; 95% CI, 49.9 to 60.5) of upadacitinib participants versus 35.7% (120 of 344; 95% CI, 30.7 to 41) dupilumab participants ($P < .01$).[43] Significantly more participants achieved EASI-100 and EASI-90 in the upadacitinib group (27.9% and 60.6%) compared to the dupilumab group (7.6% and 38.7%).[43]

Harm Outcomes

Upadacitinib was well tolerated in all 4 trials.[40-43] There was 1 death, low incidence of discontinuation, and low incidence of severe TEAEs.[40-43] TEAEs common from all upadacitinib studies were acne, nasopharyngitis, URTI, headache and elevated CPK.[40-43]

Guttman-Yassky and colleagues reported TEAEs for 79% (33 of 42) of the upadacitinib 30 mg group, 76% (32 of 42) of the upadacitinib 15 mg, 74% (31 of 42) of the upadacitinib 7.5 mg group, and 63% (25 of 40) of the placebo group.[40] Discontinuations occurred in 9.5% (4 of 42), 4.8% (2 of 42), 9.5% (4 of 42), and 7.5% (3 of 40) of participants in the upadacitinib 30 mg, upadacitinib 15 mg, upadacitinib 7.5 mg, and placebo groups, respectively.[40] Discontinuations

occurred due to infections, lymphopenia, hepatic disorder, neutropenia, and anemia.[40] The most frequent treatment related TEAEs, occurring in at least 5% of participants in any group, included URTI, acne, headache, increased CPK, nasopharyngitis, nausea, diarrhea, influenza, oropharyngeal pain, contact dermatitis, hematuria, proteinuria, ligament pain, and worsening atopic dermatitis.[40]

In the AD Up trial, overall TEAEs occurred at 72% (215 of 297), 67% (200 of 300), and 63% (190 of 303) in the upadacitinib 30 mg plus TCS, upadacitinib 15 mg plus TCS, and placebo plus TCS groups, respectively.[41] SAEs occurred in 1% (4 of 297), 2% (7 of 300) and 3% (9 of 303) of the upadacitinib 30 mg plus TCS, 15 mg plus TCS, and placebo plus TCS groups, respectively.[41] Discontinuations occurred in 5 upadacitinib 4 mg participants and 1 placebo group participant.[41] The most frequently reported TEAEs (≥ 5%) for any treatment groups was nasopharyngitis, URTI, acne, oral herpes, elevated CPK, headache, and atopic dermatitis.[41] AE discontinuations occurred in 1% (4 of 297), 1% (4 of 300), and 2% (7 of 303) of participants in the upadacitinib 30 mg, 15 mg and placebo plus TCS groups, respectively.[41]

In the Measure Up 1 and Measure Up 2 study, TEAEs occurred from 53% to 73% in each group.[42] SAEs occurred in 3% (8 of 285; 7 of 282) of upadacitinib 30 mg participants, 2% (6 of 281; 5 of 276) of upadacitinib 15 mg participants, and 3% (8 of 281; 8 of 278) of placebo in both Measure Up 1 and Measure Up 2, respectively.[42] TEAEs leading to discontinuation occurred in 1% (upadacitinib 15 mg; Measure Up 1) to 4% (upadacitinib 30 mg, upadacitinib 15 mg, and placebo) of participants.[42] Discontinuations occurred due to anemia, neutropenia, acne, and elevated CPK.[42] The most frequently reported TEAEs (≥ 5% in any treatment group) were acne, URTI, nasopharyngitis, headache, elevated CPK, and atopic dermatitis.[42]

In the Heads Up trial, participants in the upadacitinib group had a safety profile similar to that seen in other studies.[43] The overall incidence rate of TEAEs were 71.6% (249 of 348) and 62.8% (216 of 344) for upadacitinib and dupilumab, respectively.[43] Serious TEAEs occurred at a rate of 2.9% (10 of 348) for upadacitinib and 1.2% (4 of 344) for dupilumab. TEAEs leading to discontinuation occurred in 2% (7 of 348) and 1.2% (4 of 344) for upadacitinib and dupilumab, respectively.[43] There were 5 cases of COVID-19, 4 in the upadacitinib group and 1 in the dupilumab group.[43] There was 1 death in the upadacitinib group (40 year old with bronchopneumonia associated with influenza).[43] The TEAEs reported by at least 5% in either group were acne, dermatitis atopic, URTI, increased CPK, nasopharyngitis, headache and conjunctivitis.[43]

Pipeline Therapies

Baricitinib

Study Characteristics

We identified 6 RCTs in 7 publications, evaluating the use of baricitinib for moderate to severe atopic dermatitis: 1 phase-2 RCT, 3 phase-3 RCTs, 1 long-term extension study, and 1 post hoc analysis of participant-related outcomes.[18-21,45,46] For the RCTs, efficacy outcomes included validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD), EASI, Itch and Skin Pain Numerical Rating Scales, SCORAD, POEM, and DLQI.[18-21,46] Harm outcomes included incidence and severity of AEs.[18-21,46] All studies confirmed moderate to severe atopic dermatitis diagnosis with vIGA-AD of at least 3, EASI score of at least 16, and TBSA of 10% or more, for at

least 6 months to a year before initiation of study.[18-21,46] Some studies allowed concomitant TCS.[18,19,21,46] All RCT studies were rated as having a *low to high* risk of bias.[18-21,46] Table 12 provides an overview of the pertinent study characteristics.

Table 12. Study Characteristics: Baricitinib for Atopic Dermatitis

Author, Year Trial Number Trial Name Risk of Bias	Participants	Product, Dose, Frequency	Study Design	Duration
Guttman-Yassky et al., 2019[18] NCT02576938 Moderate	N = 124	Baricitinib 2 mg daily, n = 37 Baricitinib 4 mg daily, n = 38 Placebo daily, n = 49	Randomized, double-blind, phase 2, placebo-controlled trial	16 weeks
Simpson et al., 2020[21] NCT03334396 BREEZE-AD1 NCT03334422 BREEZE-AD2 Moderate	BREEZE-AD1, N = 624 BREEZE-AD2, N = 615	Baricitinib 1 mg daily, n = 127 (BREEZE-AD1), n = 125 (BREEZE-AD2) Baricitinib 2 mg daily, n = 123 (BREEZE-AD1), n = 123 (BREEZE-AD2) Baricitinib 4 mg daily, n = 125 (BREEZE-AD1), n = 123 (BREEZE-AD2) Placebo daily, n = 249 (BREEZE-AD1), n = 244 (BREEZE-AD2)	Randomized, double-blind, phase 3, placebo-controlled, parallel-group	16 weeks
Reich et al., 2020[19] Wollenberg et al., 2021[45] NCT03733301 BREEZE-AD7 Moderate	N = 329	Baricitinib 2 mg daily and TCS, n = 109 Baricitinib 4 mg daily and TCS, n = 111 Placebo daily and TCS, n = 109	Randomized, double-blind, placebo-controlled, phase 3, clinical trial	16 weeks
Simpson et al, 2021[20] NCT03435081 BREEZE-AD5 High	N = 440	Baricitinib 1 mg daily, n = 147 Baricitinib 2 mg daily, n = 146 Placebo daily, n = 147	Randomized, double-blind, placebo-controlled, phase 3, clinical trial	16 weeks
Silverberg et al., 2021[46] NCT03334435 BREEZE-AD3 Low	N = 1,081	Baricitinib 2 mg daily, n = 54 Baricitinib 4 mg daily, n = 70	Randomized, double-blind, placebo-controlled, phase 3, long-term extension clinical trial	68 weeks

Abbreviation. TCS: topical corticosteroids.

Guttman-Yassky and colleagues conducted a double-blind, phase 2 trial to determine efficacy of once daily baricitinib in combination with TCS in adults (≥18 years) over 16 weeks.[18] For enrollment, participants needed an EASI score of at least 12, TBSA involvement of over 10%, and an atopic dermatitis diagnosis for at least 2 years.[18] Participants were randomized to baricitinib 2 mg, 4 mg, or placebo once daily and received triamcinolone 0.1% cream 4 weeks prior and during the study phase.[18] The primary outcome was the proportion of participants who achieved an EASI-50 response.[18] Secondary outcomes included change from baseline in EASI and SCORAD, proportion of participants with IGA improvement and Itch Numerical Rating Scale and DLQI scores.[18] Safety and tolerability were assessed by monitoring for AEs, vital signs, and laboratory tests.[18]

Simpson and colleagues reported results for BREEZE-AD1 and BREEZE-AD2 studies which were double-blind, phase 3 clinical trials in adults.[21] Participants received either baricitinib 4 mg, baricitinib 2 mg, baricitinib 1 mg, or placebo once daily, with TCS, over 16 weeks.[21] Participants 18 years or older were included and all participants had to have confirmed diagnosis of atopic dermatitis for at least 1 year prior to randomization or first dose of study drug and a washout period was conducted.[21] Systemic and topical treatments were allowed as rescue therapy at the investigator's discretion.[21] Emollient use was required during the trial period.[21] The BREEZE-AD1 study included 624 participants and the BREEZE-AD2 study included 615 participants.[21] The primary outcomes included the proportion of participants with a vIGA-AD score improvement.[21] Secondary endpoints included EASI-75, EASI-90, percentage change in EASI, Skin Pain Numerical Rating Scale, Itch Numerical Rating Scale, change in Atopic Dermatitis Sleep Scale (ADSS).[21] Participant-reported outcomes included POEM score and DLQI score.[21] Safety and tolerability were assessed by monitoring for TEAEs, vital signs, and laboratory tests at all scheduled visits.[21]

The BREEZE-AD5 study was conducted to assess the efficacy and safety of baricitinib 2 mg and 1 mg monotherapy in adults who were intolerant or nonresponsive to topical therapy.[20] In this RCT, topical and systemic therapy was discontinued prior to randomization and not allowed for the duration of the study except as rescue therapy.[20] There were 440 participants randomized from 81 centers in the USA and Canada.[20] The primary endpoint (not determined before study initiation, but before database lock and finalization of statistical plan) was the proportion of participants achieving EASI-75 at week 16.[20] The vIGA-AD was the key secondary endpoint along with the EASI-50, Itch and Skin Pain Numerical Rating Scales, SCORAD-75, ADSS, POEM, and DLQI.[20] All TEAEs were assessed throughout the duration of the study along with laboratory tests, vital signs, and other safety assessments.[20]

The BREEZE-AD7 study was an RCT comparing the efficacy and safety of baricitinib 4 mg and 2 mg in combination with TCS therapy in adults (≥ 18 years) with moderate to severe atopic dermatitis.[19] All participants concomitantly received moderate- or low-potency TCS along with daily emollients.[19] After 2 weeks of treatment, rescue therapy was allowed for worsening atopic dermatitis symptoms. In some countries, topical calcineurin inhibitors, crisaborole, or both could be used instead of TCS.[19] The primary outcome was the proportion of participants with a vIGA-AD score improvement at week 16.[19] Secondary outcomes included EASI-75, EASI-90, SCORAD-75, Itch and Skin Pain Numerical Rating Scale, and ADSS at various time points and

end of study (week 16).[19] All TEAEs were assessed by laboratory monitoring, vital signs, and clinical assessments at scheduled study visits.[19]

Wollenberg and colleagues reported the results of health-related QoL outcomes (HRQoL) in participants from the BREEZE-AD7 trial.[45] These participants reported measures of HRQoL included the DLQI (≥ 4 point improvement), Work Productivity and Activity Impairment-atopic dermatitis (WPAI-AD) questionnaire, PROMIS, and the Patient Benefit Index (PBI).[45] Since translations were not available in all countries for the PROMIS and PBI, these results did not include all the participants.[45]

A post hoc analysis by Buhl and colleagues reported the effect of baricitinib on itch and sleep disturbance during the first week of therapy in participants from BREEZE-AD1, BREEZE-AD2, and BREEZE-AD7.[67] Participants reported symptoms in electronic diaries and completed the Itch Numerical Rating Scale and ADSS.[67]

The BREEZE-AD3 study was a noncomparative, long-term extension (52 weeks) study by Silverberg and colleagues.[46] Participants who were responders or partial responders in the BREEZE-AD1 and BREEZE-AD2 studies were allowed to enroll in this 68-week long-term efficacy trial.[46] Responders achieved a vIGA-AD score of 0 or 1 and never received rescue therapy.[46] Partial responders achieved a vIGA-AD score of 2 and never received rescue therapy.[46] The primary endpoint was proportion of participants who achieved improvement in vIGA-AD at weeks 32, 52, and 68.[46] Secondary endpoints included EASI-75, Itch Numerical Rating Scale, Skin Pain Numerical Rating Scale, ADSS, and change in vIGA-AD, EASI-75, and itch NRS.[46] A total of 1,081 participants enrolled in BREEZE-AD3.[46] Of these, 221 were classified as responders or partial responders and entered the analysis.[46]

Efficacy Outcomes

Baricitinib 4 mg and 2 mg demonstrated efficacy over placebo in almost all outcome measures.[19-21] In most instances, the baricitinib 4 mg showed greater efficacy than the baricitinib 2 mg.[18-21]

In the primary outcome of EASI-50, Guttman-Yassky and colleagues reported no significant difference between baricitinib plus TCS and placebo plus TCS.[18] Reductions in EASI were statistically significant for the baricitinib groups ($P < .01$).[18] The change in SCORAD at week 16 was 47% ($P \leq .01$) for baricitinib 4 mg plus TCS, 41% ($P < .01$) for baricitinib 2 mg plus TCS, and 21% for placebo.[21] Improvement in DLQI score was observed for both treatment groups; statistical significance was seen at week 4.[18]

At week 16 in BREEZE-AD1 and BREEZE-AD2, baricitinib as monotherapy achieved a significant improvement in vIGA-AD response versus placebo.[21] For BREEZE-AD1, 16.8% ($P \leq .01$) of the baricitinib 4 mg group, 11.4% ($P \leq .05$) of the 2 mg group, 11.8% ($P \leq .05$) of 1 mg group, and 4.8% of the placebo group achieved an improvement in vIGA-AD.[21] For BREEZE-AD2, 13.8% ($P \leq .01$) of the baricitinib 4 mg group, 10.6% ($P \leq .05$) of the 2 mg group, 8.8% of the 1 mg group, and 4.5% of the placebo group achieved an improvement in vIGA-AD.[21] The proportions of participants who had an EASI-75 response were 24.8% ($P \leq .01$), 18.7% ($P \leq .01$), 17.3% ($P \leq .05$), and 8.8% for baricitinib 4 mg, baricitinib 2 mg, baricitinib 1 mg, and placebo as monotherapy, respectively.[21] Mean change in POEM from baseline was −7.8 ($P \leq .001$) for baricitinib 4 mg, −6.3 ($P \leq .01$) for baricitinib 2 mg, −5.3 ($P \leq .05$) for baricitinib 1 mg, and −2.7 for placebo.[21]

The efficacy of baricitinib 2 mg monotherapy was reported in the BREEZE-AD5 study by Simpson and colleagues.[20] Baricitinib 1 mg did not meet the primary or secondary endpoints in this trial and statistics were not reported.[20] For the primary endpoint of EASI-75, the proportion of participants achieving this was 29.5% ($P \leq .01$), 12.9%, and 8% for the baricitinib 2 mg, baricitinib 1 mg, and placebo groups, respectively.[20] The vIGA-AD was achieved for 24% of baricitinib 2 mg participants and 5% of placebo participants ($P < .01$).[20] The total EASI percent change from baseline was −54.37 (95% CI, −33.85 to −6.75), −46.66 (95% CI, −26.54 to 1.36), and −34.07 for baricitinib 2 mg, baricitinib 1 mg, and placebo, respectively.[20] The proportion of participants achieving EASI-50 and SCORAD-75 for the baricitinib 2 mg group was 34.9% (51 of 146; 95% CI, 27.7 to 43; $P \leq .01$) and 14.4% (21 of 146; 95% CI, 9.6 to 21; $P \leq .01$), respectively.[20] The change in POEM and DLQI score for baricitinib 2 mg was −7.44 (95% CI, −7.70 to −1.84; $P \leq .01$) and −7.46 (95% CI, −5.83 to −1.16; $P \leq .01$), respectively.[20]

In the BREEZE-AD7 study, efficacy was reported with baricitinib 4 mg but not with baricitinib 2 mg.[19] At week 16, the vIGA-AD improvement response was 31% (34 of 111; 95% CI, 1.4 to 5.6; $P = .004$) for the baricitinib 4 mg group, 24% (26 of 109; 95% CI, 0.9 to 3.9; $P = .08$) for the 2 mg group, and 15% (16 of 109) for the placebo group.[19] The EASI-75 response rate at week 16 was 48% (53 of 111; 95% CI, 1.8 to 6; $P < .01$), 43% (47 of 109; 95% CI, 1.4 to 4.8) and 23% (25 of 109) for abrocitinib 2 mg, 1 mg, and placebo, respectively.[19] Other secondary endpoints in which baricitinib 4 mg showed statistically significant improvement from placebo included the EASI score change from baseline, Itch Numerical Rating Scale at week 4 and 16, and the Skin Pain Numerical Rating Scale.[19]

The HRQoL outcomes improved overall in the BREEZE-AD7 participants as reported by Wollenberg and colleagues.[45] The rate of rescue therapy was 5.4%, 4.6%, and 9.2% in the baricitinib 4 mg plus TCS group, baricitinib 2 mg plus TCS group, and placebo plus TCS group, respectively.[45] Significant improvements in the DLQI occurred at week 2 and was sustained through week 16.[45] The percentage of participants with improvement at week 16 was 73% ($P \leq .01$), 61%, and 53% for baricitinib 4 mg plus TCS, baricitinib 2 mg plus TCS, and placebo plus TCS, respectively.[45] The WPAI-AD change from baseline at week 16 was −27.3 ($P \leq .01$) for baricitinib 4 mg plus TCS, −26.6 ($P \leq .01$) for baricitinib 2 mg plus TCS, and −16.8 for placebo plus TCS.[45] The PROMIS Itch demonstrated improvements from baseline for scratching behavior, itch interference, mood/sleep and sleep-related impairment in both the baricitinib 4 mg and baricitinib 2 mg groups.[45] PBI scores demonstrated that baricitinib 4 mg and 2 mg groups had greater goal attainment for social impairment, psychological impairment, physical impairment and confidence in healing.[45]

Baricitinib improvements in itch and sleep were reported by Buhl and colleagues.[67] The Itch Numerical Rating Scale started improving from day 2 and continued through day 7.[67] The baricitinib 4 mg group demonstrated the greatest improvement at day 7 with change of −25.7%, −18.4%, and −37.8% in Itch Numerical Rating Scale score for the BREEEZE-AD1, BREEZE-AD2 and BREEZE-AD7, respectively.[67] Improvements in ADSS score for ability to fall asleep, nightly awakenings, and returning to sleep improved from day 2 through day 7 with baricitinib groups.[67] The greatest improvements were seen with the baricitinib 4 mg groups.[67]

In BREEZE-AD3, the proportion of participants who maintained or achieved vIGA-AD scores of 0 or 1 at week 68 of continuous therapy was 47.1% for baricitinib 4 mg and 59.3% for baricitinib 2 mg.[46] The EASI-75 was 55.7% for baricitinib 4 mg and 81.5% for baricitinib 2 mg at week 68.[46] The mean change in EASI for baricitinib 4 mg was 22.9 at week 16 and −20 at week 68.[46] The mean change in EASI for baricitinib 2 mg was −20.4 at week 16 and −21.7 at week 68.[46] For baricitinib 4 mg the Itch Numerical Rating Scale and Skin Pain Numerical Rating Scale responses were maintained and stable throughout the study period, 52.5% and 61.8% at week 16, and 45.9% and 54.5% at week 32, respectively.[46] For baricitinib 2 mg, responses were 44.2% and 47.5% at week 16, and 39.5% and 45% at week 32 for the Itch and Skin Pain Numerical Rating Scales, respectively.[46]

Harm Outcomes

Guttman-Yassky and colleagues reported at least 1 TEAEs for 71% (21 of 38) of the baricitinib 4 mg plus TCS group, 46% (17 of 37) of the baricitinib 2 mg plus TCS group, and 49% (24 of 49) of the placebo group.[18] One participant in the baricitinib 4 mg group had a serious TEAE, a benign polyp in the large intestine.[18] Discontinuations occurred in 13% (5 of 38), 3% (1 of 37), and 10% (5 of 49) of participants in the baricitinib 4 mg, baricitinib 2 mg, and placebo groups, respectively.[18] Discontinuations occurred due to lymphopenia, eczema, atopic dermatitis, neutropenia, decreased white blood cell count, abnormal lymphocytes, and headache.[18] The most frequent treatment-related TEAEs, occurring in at least 3 participants per treatment group, included headache, increased CPK, nasopharyngitis, cellulitis, lymphopenia and atopic dermatitis.[18]

For BREEZE-AD1 and BREEZE-AD2, TEAEs were reported in the range of 54 to 58% of participants in all baricitinib groups and placebo.[21] Severe TEAEs were reported in 1.6% (baricitinib 4 mg group) to 4.8% (baricitinib 1 mg group) of participants in the randomized groups.[21] The most frequently reported AEs (> 2% in any group) were nasopharyngitis, headache, URTI, and CPK elevations.[21] Overall discontinuation occurred in 1.2% of the baricitinib 4 mg, 1.6% of the baricitinib 2 mg, 3.6% of the baricitinib 1 mg and 1.2% of the placebo groups.[21] Herpes simplex and herpes zoster occurred in all groups at 0 to 7.2% during the BREEZE-AD1 and BREEZE-AD2 trial.[21]

Overall, the TEAEs for the BREEZE-AD5 study were similar among treatment groups and reported as 51% (74 of 145), 54% (79 of 147) and 49% (72 of 146) for baricitinib 2 mg, baricitinib 1 mg and placebo, respectively.[20] SAEs occurred at 1.4% (2 of 145), 0.7% (1 of 147) and 2.1% (3 of 146) for the baricitinib 2 mg, baricitinib 1 mg, and placebo, respectively.[20] The most common TEAEs (≥ 3%) that occurred in all groups included URTI, nasopharyngitis, diarrhea, nausea, UTI, and headache. Discontinuations were about 2.7% for all groups.[20]

In the BREEZE-AD7 study, overall TEAEs occurred at 58% (64 of 111), 56% (61 of 109), and 38% (41 of 108) in the baricitinib 4 mg, baricitinib 2 mg, and placebo groups, respectively.[19] Serous AEs occurred in 4% (4 of 111), 2% (2 of 109), and 4% (4 of 108) of the baricitinib 4 mg, 2 mg, and placebo groups, respectively.[19] Discontinuations occurred in 5 baricitinib 4 mg participants and 1 placebo group participant.[19] The most frequently reported TEAEs (≥ 2%) for both baricitinib groups were nasopharyngitis, URTI, diarrhea, acne, folliculitis, oral herpes, and back pain.

Discontinuation occurred in 5% (5 of 111) of participants, 0 participants, and 1% (1 of 108) of participants in the 4 mg, 2 mg, and placebo groups, respectively.[19]

Lebrikizumab

Study Characteristics

We identified 2 RCTs analyzing lebrikizumab for the treatment of moderate to severe atopic dermatitis: 1 phase-2 proof-of-concept and 1 phase-2b, double-blind, placebo-controlled trial.[27,36] Efficacy outcomes evaluated disease burden and itch through tools validated to measure atopic dermatitis including EASI and IGA.[27,36] QoL was evaluated through the DLQI and other tools.[27,36] Harm outcomes included TEAEs.[27,36] Both studies included participants 18 and older.[27,36] The phase-2 proof-of-concept trial used doses of lebrikizumab that have shown benefit for asthma treatment; we rated it as having a *low* RoB.[27] The phase-2b study expanded on the initial proof-of-concept study and included higher doses, more frequent dosing, and longer evaluation; we rated as having a *moderate* RoB due the scope and depth of sponsor involvement.[36] Table 13 offers additional information on these studies.

Table 13. Study Characteristics: Lebrikizumab for Atopic Dermatitis

Author, Year Trial Number Trial Name Risk of Bias	Participants	Product, Dose, Frequency	Study Design	Duration
Simpson et al, 2018[27] NCT02340234 Low	N = 209	Lebrikizumab 125 mg SQ single dose, n = 52 Lebrikizumab 250 mg SQ single dose, n = 53 Lebrikizumab 125 mg SQ every 4 weeks, n = 51	Randomized, double-blind, placebo-controlled, parallel, phase 2 proof-of-concept study	12 weeks 8-week safety extension
Guttman et al, 2020[36] NCT03443024 Moderate	N = 280	Lebrikizumab 125 mg SQ every 4 weeks (250 mg SQ LD), n = 73 Lebrikizumab 250 mg SQ every 4 weeks (500 mg SQ LD), n = 80 Lebrikizumab 250 mg SQ every 2 weeks (500 mg SQ LD at baseline and week 2), n = 75	Randomized, double-blind, placebo-controlled, parallel, phase 2b dose-ranging study	16 weeks 4-week and 8-week extension 16-week extension phone call

Abbreviations. SQ: subcutaneous; LD: loading dose.

Simpson and colleagues conducted a multicenter proof-of-concept study.[27] Adults with a baseline EASI of 14 or more, an IGA of 3 or more, lesions covering at least 10% TBSA, pruritus VAS score of 3 or more, and inadequate response to 1 month or more of TCS were included in the 12 week study with an 8 week safety extension.[27] Participants received subcutaneous doses of lebrikizumab or placebo.[27] Participants were randomized to lebrikizumab 125 mg single dose, 250 mg single dose, 125 mg dose every 4 weeks, or placebo.[27] In addition to lebrikizumab or placebo, participants also received twice daily, medium potency TCS.[27]

The primary outcome was EASI-50 achievement at 12 weeks.[27] Secondary outcomes included percent of participants achieving EASI-75, IGA score of 0 to 1, or SCORAD-50 at week 12.[27] The DLQI, Atopic Dermatitis Impact Questionnaire (ADIQ), and pruritus and sleep VAS change from baseline assessed quality measures.[27] Safety outcomes included TEAEs and SAEs evaluated through week 20.[27]

Guttman and colleagues conducted a follow-up study to Simpson and colleagues.[27,36] Guttman and colleagues conducted a multicenter dose-ranging study.[36] Adults with a baseline EASI of 16 or more, IGA of 3 or more, lesions covering at least 10% TBSA, and a history of 1 year of atopic dermatitis were included in the 16-week study with a 16-week safety extension.[36] Participants received subcutaneous doses of lebrikizumab or placebo.[36] Participants were randomized to lebrikizumab 125 mg every 4 weeks with a 250 mg loading dose, 250 mg every 4 weeks with a 500 mg loading dose, or 250 mg every 2 weeks with a 500 mg loading dose at baseline and at week 2.[36] Participants received either treatment or placebo every 2 weeks to maintain the double-blind nature of the study.[36] Unlike Simpson and colleagues, participants did not receive TCS; however, they could receive TCS as rescue therapy and still be included in the study.[27,36,68] Participants receiving systemic corticosteroid rescue therapy were discontinued from data collection.[36]

The primary outcome was percent reduction in EASI.[36] Secondary outcomes included percent of participants achieving an EASI-50, EASI-75, EASI-90, IGA of 0 to 1, and proportion of participants with a 4-point improvement of the PP-NRS.[36] Other secondary outcomes included percent change in TBSA, and change in Numerical Rating Scale score.[36] The POEM, DLQI, and PP-NRS change from baseline assessed quality measures.[36] Safety outcomes included TEAEs evaluated through week 32.[36]

Efficacy Outcomes

CoE for lebrikizumab was rated as *low* to *moderate*. Table 2 describes summary of GRADE findings.

Lebrikizumab showed varying improvement of EASI from baseline across all the doses used, with a clear improvement in benefit with increasing dose.[27] Lebrikizumab 125 mg and 250 mg as a single dose showed no significant difference to placebo.[27] Lebrikizumab dosed 125 mg every 4 weeks for 12 weeks showed statistically significant improvement in EASI-50 over placebo (82.4% vs. 62.3%, respectively; $P = .03$), EASI-75 over placebo (54.9% vs. 34%, respectively; $P = .04$), and SCORAD-50 over placebo (51% vs. 26.4%, respectively; $P < .01$).[27] Lebrikizumab 125 mg single dose and 125 mg every 4 weeks for 12 weeks demonstrated statistically significant improvement in sleep VAS over placebo (53.1% and 53.6% vs. 22.6%, respectively).[27]

Lebrikizumab showed statistically significant improvement in percent change of EASI from baseline to 16 weeks with 125 mg every 4 weeks (−62.3%; 95% CI, −38.6 to −3.9; $P = .02$), 250 mg every 4 weeks (−69.2%; 95% CI, −46 to −10.2; $P < .01$), and 250 mg every 2 weeks (−72.1%; 95% CI, −48.3 to −13.6; $P < .01$) over placebo.[36] Lebrikizumab 250 mg every 2 weeks was most effective and had statistically significant improvement in EASI-90 (44%; $P < .001$) and had improvements in itching scores as early as day 2 of therapy.[36] Guttman and colleagues did

not statistically compare quality measures between treatment and placebo, although all treatment doses showed large improvements in both the POEM and DLQI.[36]

Harm Outcomes

Simpson and colleagues showed no significant difference in AEs with lebrikizumab compared to placebo.[27] AEs including infections, skin infections, herpes infections, and conjunctival AE occurred more than 5% in at least 1 treatment group.[27] Safety of lebrikizumab was similar to previous studies conducted in participants with asthma at similar doses.[27] Discontinuation of the treatment and placebo was similar, which was most likely due to the twice-daily moderate dose TCS that boosted the placebo effect.[27]

Guttman and colleagues had higher rates of TEAEs due to the higher doses and loading doses used in the study.[36] Most reactions were mild to moderate with low rates of injection-site reactions, herpes virus infections, and conjunctivitis (5.7%, 3.5%, and 2.6%, respectively).[36] Upper respiratory infections, headache, injection-site pain, and fatigue occurred at a rate of 5% or more in at least 1 treatment arm with the highest being upper respiratory infections at a rate of 7.5% across all treatment groups.[36] Overall, lebrikizumab was showed to be relatively safe with no SAEs being directly related to the medication.[36]

Nemolizumab

Study Characteristics

We identified 3 studies in 6 publications analyzing nemolizumab for the treatment of moderate to severe atopic dermatitis: 3 randomized placebo-controlled, 2 post hoc, and 1 randomized uncontrolled follow-up trial.[28-30,37,69,70] Efficacy outcomes evaluated disease burden and itch through tools validated to measure atopic dermatitis including EASI and IGA.[28,29,37,70] QoL was evaluated through the DLQI, pruritus VAS and other tools.[28-30,37,69,70] Harm outcomes included TEAEs.[28-30,37] Studies were rated as *low* to *moderate* RoB.[28,29,37] Table 14 offers additional information on the nemolizumab studies.

Table 14. Study Characteristics: Nemolizumab for Atopic Dermatitis

Author, Year, Registration Number, Trial Name, Risk of Bias	Participants	Product, Dose, Frequency	Study Design	Duration
Ruzicka 2017[28] NCT01986933 Low	N = 264	Nemolizumab 0.1 mg/kg SQ every 4 weeks, n = 53 Nemolizumab 0.5 mg/kg SQ every 4 weeks, n = 54 Nemolizumab 2.0 mg/kg SQ every 4 weeks, n = 52 Nemolizumab 2.0 mg/kg SQ every 8 weeks, n = 52	Randomized, double-blind, placebo-controlled, parallel, phase 2, multicenter, dose ranging study	12 weeks (weeks 1 to 12)
Kabashima 2018[30] NCT01986933 Low	N = 191		Randomized, double-blind, phase 2, multicenter, extension study	52 weeks (weeks 12 to 64)
Mihara 2019[69] NCT01986933 Low	N = 138		Post hoc analysis	64 weeks (weeks 1 to 64)

Author, Year, Registration Number, Trial Name, Risk of Bias	Participants	Product, Dose, Frequency	Study Design	Duration
Silverberg 2020[29] NCT03100344 Moderate	N = 226	Nemolizumab 10 mg SQ every 4 weeks (20 mg LD), n = 55 Nemolizumab 30 mg SQ every 4 weeks (60 mg LD), n = 57 Nemolizumab 90 mg SQ every 4 weeks (90 mg LD), n = 57	Randomized, double-blind, placebo-controlled, parallel, phase 2b, multicenter, dose-ranging study	24 weeks 12-week follow-up
Silverberg 2021[70] NCT03100344 Moderate	N = 94		Post hoc analysis	24 weeks
Kabashima 2020[37] JapicCTI 173740 Low	N = 215	Nemolizumab 60 mg SQ every 4 weeks	Randomized, double-blind, placebo-controlled, phase 3, multicenter study	16 weeks with a 52-week open-label extension

Abbreviations. LD: loading dose; SQ: subcutaneous.

Ruzicka and colleagues conducted part A of a 2-part multicenter, phase 2, dose-ranging study.[28] Part A consisted of 12 weeks and part B consisted of a 52-week extension conducted by Kabashima and colleagues.[28,30] Ruzicka and colleagues enrolled adults with a baseline EASI of 10 or more, an IGA of 3 or more, and an itch VAS score of 50 or more (out of 100) into a 12-week study.[28] Participants were randomized to subcutaneous doses of nemolizumab 0.1 mg/kg, 0.5 mg/kg, or 2.0 mg/kg every 4 weeks, nemolizumab 2.0 mg/kg every 8 weeks, or placebo.[28] In addition to nemolizumab or placebo, participants were allowed to use emollients or localized treatments.[28] Participants could also receive rescue therapy with TCS.[28] Kabashima and colleagues conducted the 52-week extension and randomized the participants taking placebo in part A to nemolizumab 0.1 mg/kg, 0.5 mg/kg, or 2.0 mg/kg every 4 weeks.[30] The 52-week extension was not placebo-controlled.[30] Mihara and colleagues conducted a post hoc analysis of parts A and B. [69]

In part A, the primary outcome evaluated improvement in itch VAS from baseline to week 12. Secondary outcomes in part A included change from baseline to 12 weeks with EASI, SCORAD, IGA, TBSA, and sleep VAS.[28] Additional secondary outcomes were evaluated in part B and included improvement from baseline with EASI, SCORAD, IGA, TBSA, itch verbal rating scale, and sleep VAS.[30] Other secondary outcomes assessed in part B included EASI-25, EASI-50, and EASI-75, itch VAS, and SCORAD.[30] Mihara and colleagues evaluated Work Productivity and Activity Impairment (WPAI) in participants that completed WPAI questionnaires.[69]

Silverberg and colleagues conducted a multicenter, phase 2b, dose-ranging study.[29] Silverberg and colleagues included adults with severe atopic dermatitis-associated itching uncontrolled by topical agents, an IGA of 3 or more, atopic dermatitis for 2 or more years, a TBSA of at least 10%, an EASI of 12 or more, and inadequate response to TCS for the past 6 months.[29] Investigators randomized participants to 10 mg, 30 mg, or 90 mg of nemolizumab (with 20 mg, 60 mg, and 90 mg loading doses respectively) or placebo every 4 weeks for 24 weeks.[29] All

participants received low- to mid-potency TCS with moisturizer.[29] Silverberg and colleagues evaluated the primary outcome of EASI change from baseline to 24 weeks and secondary outcomes including achievement of an IGA of 0 to 1, percent change of EASI at each visit, pruritus numerical scores, change in SCORAD, and achievement of EASI-50, EASI-75, and EASI-90 at 24 weeks.[29] Silverberg and colleagues chose DLQI, HADS, and the EuroQoL 5-dimension scales as quality measures.[29] The post hoc analysis evaluated efficiency in participants with a baseline EASI score of 16 or more.[70]

Kabashima and colleagues conducted a multicenter, phase-3, study.[37] Kabashima and colleagues enrolled adolescents and adults 13 and older, weighing 30 to 120 kg, with moderate to severe atopic dermatitis, or a 3 or more on a 5-point itch scale, pruritus VAS of 50 or more (out of 100), and an EASI of 10 or more, to medium-potency TCS or topical calcineurin inhibitors for a 4 week run-in period.[37] The topical agent used was continued in addition to nemolizumab 60 mg every 4 weeks or placebo continued for a total of 16 weeks with a 52 week open-label extension.[37] TCS rescue therapy was allowed at the discretion of the investigators.[37] The primary outcome included percent change in itch VAS score.[37] Key secondary outcomes included percent change in EASI from baseline, a 4 or less on DLQI, 4 or more point change in DLQI, and a 7 or less on the Insomnia Severity Index at 16 weeks.[37]

Efficacy Outcomes

CoE for nemolizumab was rated as *very low* to *moderate*. Table 2 describes summary of GRADE findings.

Nemolizumab compared to placebo showed improvement in pruritus VAS score, at the 0.1 mg/kg (−43.7 vs. −20.9, respectively; 95% CI, −53.4 to −34.0; $P < 0.01$), 0.5 mg/kg (−59.8 vs. −20.9, respectively; 95% CI, −69.4 to −50.3; $P < .01$), and 2.0 mg/kg (−63.1 vs. −20.9, respectively; 95% CI, −72.9 to −53.3; $P < .01$) at week 12.[28] Kabashima and colleagues showed similar improvement in percent change of pruritus VAS score from baseline to week 16 between nemolizumab 60 mg every 4 weeks and placebo (difference, −21.5; 95% CI, −30.2 to −12.7; $P < .01$).[37]

Silverberg and colleagues and Kabashima and colleagues demonstrated a statistically significant change in EASI from baseline and achievement of a prespecified percent reduction in EASI.[29,37,70] All other studies only evaluated changes in EASI without measuring the significance.[28,30] Silverberg and colleagues showed significant reduction in EASI with the 30 mg every 4 week dose of nemolizumab over placebo (−68.8% vs. −52.1%, respectively; $P = .02$) at week 24.[29] Silverberg and colleagues showed in the post hoc analysis that the benefit was as early as week 1 ($P \leq .01$) and significant achievement of EASI-75 and EASI-90 over placebo (50% vs. 15.9% and 36% vs. 6.8%, respectively; $P < .01$).[70] Kabashima and colleagues showed similar reductions in EASI from baseline to week 16 with nemolizumab 60 mg every 4 weeks over placebo (−45.9% vs. −33.2%, respectively; 95% CI, −24 to −1.3).[37] Ruzicka and colleagues did not test for significant difference of EASI with nemolizumab; however, the most benefit was demonstrated in the 0.5 mg/kg every 4 week dose over placebo (−42.3% vs. −26.6%, respectively).[28] Kabashima and colleagues showed a 75.8% improvement in EASI at week 64 with nemolizumab 0.5 mg/kg every 4 weeks.[30]

Silverberg and colleagues showed significant improvements in SCORAD with nemolizumab 10 mg every 4 weeks (−34.6 vs. −25; *P* = .02) and 30 mg every 4 weeks (−37.8 vs. −25; *P* = .01) over placebo.[29] The 90 mg every 4 week dose of nemolizumab did not show benefit in reduction SCORAD (*P* = .06).[29] Silverberg and colleagues showed, in the post hoc analysis, a steady reduction in SCORAD scores across study visits in the nemolizumab group, with significant difference from placebo at all visits beginning with week 1 (−26.7% vs −13.3%, respectively, *P* < .01).[70] At week 16, SCORAD improvements were −57.1% in the nemolizumab 30 mg group compared with −28.2% in the placebo group (*P* < .01).[70] Ruzicka and colleagues did not test for significance of SCORAD; however, they did show a dose dependent improvement with 2.0 mg/kg every 4 weeks having the greatest improvement over placebo (−39.8 vs. −18.5, respectively).[28] Kabashima and colleagues showed a 64% improvement in SCORAD at week 64 with nemolizumab 0.5 mg/kg every 4 weeks.[30]

Silverberg and colleagues showed no significant achievement an IGA of 0 to 1 at week 24; however, there was a significant difference at week 16 with nemolizumab 30 mg every 4 weeks over placebo (33.3% vs. 12.3%; *P* = .01).[29] Silverberg and colleagues showed, in the post hoc analysis, achievement of an IGA of 0 to 1 at week 16 with nemolizumab 30 mg every 4 weeks over placebo (32% vs. 6.8%, respectively; 95% CI, 10.1 to 40.1; *P* = .003).[70] Ruzicka and colleagues did not test for significance with achieving a 2-point reduction in IGA; however, they did show the most improvement with 0.5 mg/kg every 4 weeks over placebo (38% vs. 11%, respectively).[28] Kabashima and colleagues showed an achievement of IGA 0 to 1 in 32% of participants at week 64 with nemolizumab 0.5 mg/kg every 4 weeks.[30]

Kabashima and colleagues showed significant improvement in the percentage of participants with a DLQI score of 4 or less at week 16 on nemolizumab 60 mg every 4 weeks over placebo (40% vs. 22%, respectively; 95% CI, 2 to 3).[37] In the post hoc analysis, Silverberg and colleagues showed improvement in DLQI at weeks 2 and 12 with nemolizumab 30 mg every 4 weeks; at week 2, DLQI was reduced by −9.0 in the nemolizumab group versus −4.5 in the placebo group (*P* < .01).[70] Kabashima and colleagues showed an 81% achievement of a DLQI score reduction of 4 or more points at week 64 with nemolizumab 0.5 mg/kg every 4 weeks.[30]

Mihara and colleagues only showed a benefit with nemolizumab 2.0 mg/kg every 4 weeks in percent activity impairment (−41.9%; *P* < .01).[69] All other WPAI outcomes were nonsignificant.[69]

Harm Outcomes

Ruzicka and colleagues showed 1 or more AE in 67% to 77% and 1 or more SAE in 2 to 6% of the treatment arms. Most common reactions occurring with nemolizumab included exacerbation of atopic dermatitis (17 to 21%), nasopharyngitis (10 to 17%), URTI (2 to 10%), peripheral edema (4 to 10%), and elevated blood creatinine kinase (4 to 8%).[28] Most AEs had similar rates in placebo aside from exacerbation of atopic dermatitis and peripheral edema, which had higher rates in the treatment arms.[28] In the long-term follow-up, Kabashima and colleagues showed the most common AE to be nasopharyngitis (27%), exacerbation of atopic dermatitis (25%), increased blood creatine phosphokinase (11%), URTI (9%), headache (8%), peripheral edema (6%), and impetigo (6%).[30] The highest incidence of events occurred in the 2.0 mg/kg every 4 weeks treatment arm.[30]

Silverberg and colleagues showed similar AE compared to placebo.[29] The most common AE reported included nasopharyngitis (26.6%), URTI (8.3%), herpes infection (7.1%), atopic dermatitis (24.9%), respiratory, thoracic, and mediastinal disorders (18.3%), and asthma (11.2%).[29] Asthma showed a dose-dependent effect with a linear increase in occurrence with increased dose.[29]

Kabashima and colleagues showed 71% of participants in each group reported an AE.[37] Comparing nemolizumab 60 mg to placebo, most AE were mild (63 vs 62% respectively) and moderate (22 vs 19%, respectively), with 3 severe events in the treatment group including, Meniere's disease, acute pancreatitis, and atopic dermatitis.[37] Most common AE in the nemolizumab group included atopic dermatitis (23%), nasopharyngitis (13%), abnormal cytokine (7%), increased blood creatinine kinase (3%), and acne (1%).[37] AEs of special interest included injection-related reactions (8%), worsening atopic dermatitis (24%), skin infection (7%), and elevated creatinine kinase (3%).[37]

Tradipitant

We identified no eligible studies that assessed tradipitant for moderate to severe atopic dermatitis.

Ongoing Studies

We identified 32 ongoing studies that would potentially be eligible for this topic, which include:

- 4 studies with abrocitinib[71-74]
- 4 studies with baricitinib[75-78]
- 2 studies with crisaborole[79,80]
- 4 studies with dupilumab[81-84]
- 5 studies with lebrikizumab[85-89]
- 4 studies with nemolizumab[90-93]
- 1 study with ruxolitinib[94]
- 2 studies with tradipitant[95,96]
- 4 studies with tralokinumab[97-100]
- 2 studies with upadacitinib[101,102]

Study sizes range from 25 to 3,000 participants, with most studies enrolling between 200 and 1,000 participants. Most studies are scheduled to be completed between 2021 and 2023 with some long-term extension studies expected to continue until at least 2027. Many of these studies use EASI-75 and an IGA of 0 or 1 as the primary clinical outcome. CDLQI, DLQI and AEs are also commonly assessed. Table 15 summarizes these studies.

Table 15. Ongoing Studies for Atopic Dermatitis

Study Number Study Title Study Name	Intervention and Comparator Study Design	Estimated Completion Date Estimated Enrollment	Outcomes
Abrocitinib			
NCT03627767[74] Study to investigate efficacy and safety of PF-04965842 in subjects aged 12 years and over with moderate to severe atopic dermatitis with the option of rescue treatment in flaring subjects	Abrocitinib vs. placebo RCT	October 2020 (actual) N = 1,235 (actual)	• Loss of response • Time to loss of response • IGA: 0 or 1 • EASI-50 • EASI-75 • SCORAD • DLQI or CDLQI as appropriate
NCT04345367[71] Study of abrocitinib compared with dupilumab in adults with moderate to severe atopic dermatitis on background topical therapy	Abrocitinib vs. dupilumab RCT	July 2021 (actual) N = 728 (actual)	• Change in PP-NRS • EASI • IGA • SCORAD • TBSA affected • DLQI • TEAEs • SAEs
NCT03915496[73] Study evaluating the mechanism of action of PF-04965842 monotherapy for moderate-to-severe atopic dermatitis JADE MOA	Abrocitinib vs. placebo RCT	December 2021 (actual) N = 37 (actual)	• Biomarkers • Change in itching
NCT03422822[72] Study to evaluate efficacy and safety of PF-04965842 with or without topical medications in subjects aged 12 years and older with moderate to severe atopic dermatitis JADE EXTEND	Abrocitinib vs. placebo RCT	February 2024 N = 3,000	• TEAEs • SAEs leading to discontinuation • Change in ECG measurements • IGA • EASI • Body surface area affected • DLQI or CDLQI as appropriate • Steroid-free days
Baricitinib			
NCT03559270[78] A study of baricitinib (LY3009104) in participants with moderate to severe atopic dermatitis BREEZE-AD6	Baricitinib Open-label extension study	February 2022 N = 380	• EASI-75 • IGA: 0 or 1 • TBSA involvement of ≤ 3%

Study Number Study Title Study Name	Intervention and Comparator Study Design	Estimated Completion Date Estimated Enrollment	Outcomes
NCT03428100[75] A long-term study of baricitinib (LY3009104) with TCS in adults with moderate to severe atopic dermatitis that are not controlled with cyclosporine or for those who cannot take oral cyclosporine because it is not medically advisable **BREEZE-AD4**	Baricitinib vs. placebo vs. TCS **RCT**	June 2023 (actual) **N = 463 (actual)**	• EASI-75 at 16 weeks • IGA: 0 or 1 at 16 weeks • EASI-90 • SCORAD-75 • ADSS • Steroid-free days
NCT03334435[76] A study of long-term baricitinib (LY3009104) therapy in atopic dermatitis **BREEZE-AD3**	Baricitinib vs. placebo **RCT**	September 2023 **N = 1,760**	• IGA: 0 or 1 at 16 weeks • IGA: 0 or 1 at 36 weeks • IGA: 0 or 1 at 52 weeks • EASI-75
NCT03952559[77] A study of baricitinib (LY3009104) in children and adolescents with atopic dermatitis BREEZE-AD-PEDS	Baricitinib vs. placebo vs. TCS **RCT**	January 2027 **N = 465**	• IGA: 0 or 1 at 16 weeks • Pharmacokinetic assessments • EASI-75 • SCORAD • TCS usage • DLQI or CDLQI as appropriate
Crisaborole			
NCT03645057[80] PROs & caregiver burden in children with atopic dermatitis ASPIRE	Crisaborole vs. tacrolimus RCT	August 2021 (actual) N = 92 (actual)	• Pediatric Itch Short Form • Pain Interference-Pediatric adaptive test • CDQLI • EASI • Caregiver Burden Inventory
NCT03832010[79] Steroid-reducing effects of crisaborole	Crisaborole vs. TCS vs. Aquaphor RCT	December 2022 N = 60	• Steroid usage • Steroid refills • SCORAD • CDLQI or DLQI as appropriate • Severity of itching
Dupilumab			
NCT03912259[82] Evaluation of dupilumab in Chinese adult participants with moderate to severe atopic dermatitis	Dupilumab vs. placebo vs. emollient RCT	February 2020 (actual) N = 165 (actual)	• IGA: 0 or 1 at 16 weeks • EASI-75 • DLQI • Reduction in weekly average of peak daily Pruritus NRS Score

Study Number Study Title Study Name	Intervention and Comparator Study Design	Estimated Completion Date Estimated Enrollment	Outcomes
NCT01949311[81] Open-label study of dupilumab in participants with atopic dermatitis	Dupilumab Open-label follow-up for participants who participated in previous dupilumab trials	July 2022 N = 2,733 (actual)	• TEAEs • SAEs • IGA • EASI-75 • Percent change in EASI
NCT04512339[83] Dupilumab in severe chronic hand eczema DUPSHE	Dupilumab vs. placebo RCT	December 2022 N = 30	• HECSI • Pruritus NRS • DLQI • Improvement in work productivity • AEs • Pain NRS
NCT04895423[84] Evaluation of the effectiveness and safety of immunosuppressive and biological therapy of atopic dermatitis in childhood	Dupilumab vs. mycophenolate mofetil vs. cyclosporine vs. methotrexate RCT	July 2023 N = 160	• SCORAD • NRS • AEs • CLDQI
Lebrikizumab			
NCT04250337[87] Safety and efficacy of lebrikizumab (LY3650150) in combination with topical corticosteroid in moderate-to-severe atopic dermatitis ADhere	Lebrikizumab vs. placebo vs. TCS RCT	September 2021 (actual) N = 228 (actual)	• IGA: 0 or 1 at 16 weeks • EASI-75 • SCORAD • DLQI or CDLQI as appropriate • Change from baseline to week 16 in percent TBSA • Sleep changes • Change in Pruritus NRS
NCT04146363[85] Evaluation of the efficacy and safety of lebrikizumab (LY3650150) in moderate to severe atopic dermatitis ADvocate1	Lebrikizumab vs. placebo RCT	May 2022 N = 400	• IGA: 0 or 1 at 16 weeks • EASI-75 • SCORAD • DLQI or CDLQI as appropriate • Change from baseline to week 16 in percent TBSA • Sleep changes
NCT04178967[88] Evaluation of the efficacy and safety of lebrikizumab (LY3650150) in moderate to severe atopic dermatitis ADvocate2	Lebrikizumab vs. placebo RCT	June 2022 N = 400	• IGA: 0 or 1 at 16 weeks • Pharmacokinetic assessments • EASI-75 • SCORAD • DLQI or CDLQI as appropriate • Sleep changes

Study Number Study Title Study Name	Intervention and Comparator Study Design	Estimated Completion Date Estimated Enrollment	Outcomes
NCT04760314[86] A study of lebrikizumab (LY3650150) in combination with TCS in Japanese participants with moderate-to-severe atopic dermatitis ADhere-J	Lebrikizumab vs. placebo vs. TCS RCT	January 2023 N = 280	• IGA: 1 or 0 and a reduction of ≥ 2 points at 16 weeks • EASI-75 • EASI-90 • Change in Itch NRS
NCT04392154[86] Long-term safety and efficacy study of lebrikizumab (LY3650150) in participants with moderate-to-severe atopic dermatitis ADjoin	Lebrikizumab Extension study (both blinded and open-label depending on parent study assignment)	May 2024 N = 1,000	• Discontinuation due to AEs • IGA: 1 or 0 • EASI-75
Nemolizumab			
NCT04562116[90] A study to assess the effects of nemolizumab on cytochrome P450 substrates in participants with moderate-to-severe atopic dermatitis	Nemolizumab with CYP450 substrates Open-label drug interaction study	March 2022 N = 25	• AUC • AEs • TEAEs
NCT03985943[92] Efficacy and safety of nemolizumab in subjects with moderate-to-severe atopic dermatitis	Nemolizumab vs. placebo RCT	December 2022 N = 750	• IGA: 0 or 1 at 16 weeks • EASI-75 • Peak Pruritus NRS
NCT03989349[93] Efficacy and safety of nemolizumab in subjects with moderate-to-severe atopic dermatitis	Nemolizumab vs. placebo RCT	December 2022 N = 750	• IGA: 0 or 1 at 16 weeks • EASI-75 • Peak Pruritus NRS
NCT03989206[91] Long-term safety and efficacy of nemolizumab with moderate-to-severe atopic dermatitis	Nemolizumab Open-label extension study	September 2023 N = 1,300	• TEAEs • SAEs • IGA: 0 or 1 • EASI-75 • SCORAD
Ruxolitinib			
NCT04921969[94] A study to assess the efficacy and safety of ruxolitinib cream in children with atopic dermatitis TRuE-AD3	Ruxolitinib vs. placebo RCT	October 2023 N = 250	• IGA: 1 or 0 and a reduction of ≥ 2 points at 16 weeks • EASI-75 • TEAEs • Itch NRS improvement

Study Number Study Title Study Name	Intervention and Comparator Study Design	Estimated Completion Date Estimated Enrollment	Outcomes
Tradipitant			
NCT03568331[95] Evaluating the effects of tradipitant vs. placebo in atopic dermatitis EPIONE	Tradipitant vs. placebo RCT	February 2020 (actual) N = 375 (actual)	• Reduction in worst itch measured by NRS • SCORAD • EASI • IGA • AEs
NCT04140695[96] Evaluating the effects of tradipitant vs. placebo in atopic dermatitis EPIONE2	Tradipitant vs. placebo RCT	December 2020 N = 200	• Reduction in worst itch measured by NRS • SCORAD • EASI • IGA • AEs
Tralokinumab			
NCT03761537[97] Tralokinumab in combination with TCS in subjects with severe atopic dermatitis ECZTRA 7	Tralokinumab vs. placebo RCT	September 2020 (actual) N = 277 (actual)	• EASI-75 • SCORAD • DLQI • IGA: 0 or 1 at 16 and 26 weeks • AEs
NCT03526861[98] Tralokinumab monotherapy for adolescent subjects with moderate to severe atopic dermatitis ECZTRA 6	Tralokinumab vs. placebo RCT	March 2021 (actual) N = 301 (actual)	• IGA: 0 or 1 at 16 weeks • EASI-75 at 16 weeks • SCORAD • CDLQI • AEs • EASI
NCT04587453[100] Tralokinumab in combination with TCS in Japanese subjects with moderate-to-severe atopic dermatitis ECZTRA 8	Tralokinumab vs. placebo vs. TCS RCT	July 2021 (actual) N = 106 (actual)	• IGA: 0 or 1 at 16 and 26 weeks • EASI-75 • SCOARD • DLQI • AEs • Presence of antidrug antibodies
NCT03587805[99] Long-term extension trial in subjects with atopic dermatitis who participated in previous tralokinumab trials ECZTEND	Tralokinumab Open-label extension study	June 2024 N = 1,600	• AEs • IGA: 0 or 1 up to 248 weeks • EASI-75
Upadacitinib			
NCT03661138[102] A study to evaluate safety of upadacitinib in combination with TCS in adolescent and adult	Upadacitinib vs. placebo vs. TCS	August 2022 N = 272	• AEs up to 141 weeks

Study Number Study Title Study Name	Intervention and Comparator Study Design	Estimated Completion Date Estimated Enrollment	Outcomes
participants with moderate to severe atopic dermatitis Rising Up			
NCT04195698[101] Open-Label extension study of upadacitinib in adult participants with moderate to severe atopic dermatitis	Upadacitinib Open-label extension study	March 2023 N = 485	• AEs up to 52 weeks

Abbreviations. ADSS: Atopic Dermatitis Symptom Score; AUC: area under the curve; CDQLI: Children's Dermatology Life Quality Index; DLQI: Dermatology Life Quality Index; EASI: Eczema Area Severity Index; ECG: electrocardiogram; HECSI: Hand Eczema Severity Index; IGA: Investigators Global Assessment; NRS: Numerical Rating Scale; PP-NRS: Peak Pruritus Numerical Rating Scale; PROs: patient reported outcomes; RCT: randomized controlled trial; SAE: serious adverse event; SCORAD: scoring atopic dermatitis; TCS: topical corticosteroids; TEAE: treatment emergent adverse event; TBSA: total body surface area.

Discussion

Existing therapies for moderate-to-severe atopic dermatitis include a variety of pharmaceuticals with various routes of administration, including orally administered products, topical creams, and subcutaneous injections. Older therapies such as azathioprine and cyclosporine are effective, but carry the risks of significant AEs such as systemic immunosuppression. Our review demonstrates that newer treatment options, such as crisaborole and dupilumab, are effective and improve burden of disease and QoL. Tacrolimus and pimecrolimus have also demonstrated superior efficacy to placebo and therapeutic equivalence in a previous DERP review.

Beyond those positive findings, azathioprine showed mixed long-term efficacy with many participants discontinuing treatment when followed for extended time periods due to AEs. Studies for cyclosporine highlighted the fact that there were not enough RCTs to provide synthesized evidence for each of those comparator groups (i.e., methotrexate, EC-MPS, prednisolone, tacrolimus, BDP, and placebo). Further, the majority of these studies were rated as having either *high* or *moderate* RoB, indicating the study findings should be interpreted with caution. Most comparator groups had similar efficacy when compared to cyclosporine, but in general, they had fewer safety concerns than for cyclosporine.

A newer FDA-approved treatment for atopic dermatitis is topical ruxolitinib, which showed good efficacy with high rates of response as assessed by EASI and IGA. This was demonstrated in large studies with *high* CoE.

Abrocitinib, baricitinib, and upadacitinib are oral JAK inhibitors recently approved or in the pipeline for treatment of atopic dermatitis. Abrocitinib and baricitinib generally had similar response rates as assessed by EASI-75 with 29% to 40% of participants achieving goal by week 12 or week 16. Upadacitinib demonstrated higher EASI-75 response rates with 60% to 70% of participants achieving goal. Nasopharyngitis, headache, and upper respiratory infections were

the most commonly reported AEs for this drug class. Abrocitinib is currently FDA-approved for treatment of rheumatoid arthritis.

Lebrikizumab, nemolizumab, and tralokinumab are injectable monoclonal antibodies that target key drivers of underlining inflammation. Completed studies with lebrikizumab show a dose-dependent benefit with higher doses eliciting a greater reduction disease burden. Lebrikizumab improves efficacy measures when compared with placebo; however, the effect sizes were relatively small and phase-3 studies are needed to show the true benefit of lebrikizumab. For nemolizumab, completed studies show inconsistent results in efficacy and quality measures between different doses. So far, the evidence demonstrated a moderate dose of nemolizumab being as effective or more effective than higher doses, with fewer AEs. Nemolizumab appears to be a safe and effective alternative for individuals who find no benefit with topical therapies. Tralokinumab was shown to be superior to placebo in efficacy and quality measures when used for short durations. Demonstrated efficacy with long-term use is inconsistent and further studies are needed to determine the efficacy over 24 weeks of use. Tralokinumab appears to be safe, with AEs similar to placebo.

Most studies in our review were short in duration, evaluating 8 to 16 weeks of initial therapy. While this is a useful assessment, atopic dermatitis is a chronic disease and long-term follow-up is needed to assess long-term efficacy and safety of these therapies. Omalizumab and pimecrolimus offered the longest follow-up periods and did show continued efficacy for up to 5 years. Studies varied in whether TCS was included as either a comparator, exclusion criterion, or rescue medication. Baricitinib and upadacitinib are notable in that they included TCS within their study participants. This is important, as TCS are a common treatment for atopic dermatitis. Lastly, atopic dermatitis and other similar conditions often rely on surrogate or self-reported measures to evaluate efficacy and safety. DERP participants might consider the validity of certain outcomes and determine which are likely to capture most accurately the improvements for individuals with atopic dermatitis. These outcomes could be used in coverage criteria or prior authorization processes to optimize efficacy and safety for their beneficiaries.

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Appendix A. Methods

Please find Appendix A in the accompanying appendices document.

Appendix B. Full Evidence Tables

Please find Appendix B in the accompanying appendices document.

Appendix C. Bibliography of Included Studies

Please find Appendix C in the accompanying appendices document.

Appendix D. Bibliography of Excluded Studies

Please find Appendix D in the accompanying appendices document.

Suggested citation: Lindsey W, Fahim S, Chung A, Smithgall S, Zao C, Grabowsky A. *Pharmaceutical treatments for atopic dermatitis: an update*. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2022.

Conflict of Interest Disclosures: No authors have conflicts of interest to disclose. All authors have completed and submitted the Oregon Health & Science University form for Disclosure of Potential Conflicts of Interest, and none were reported.